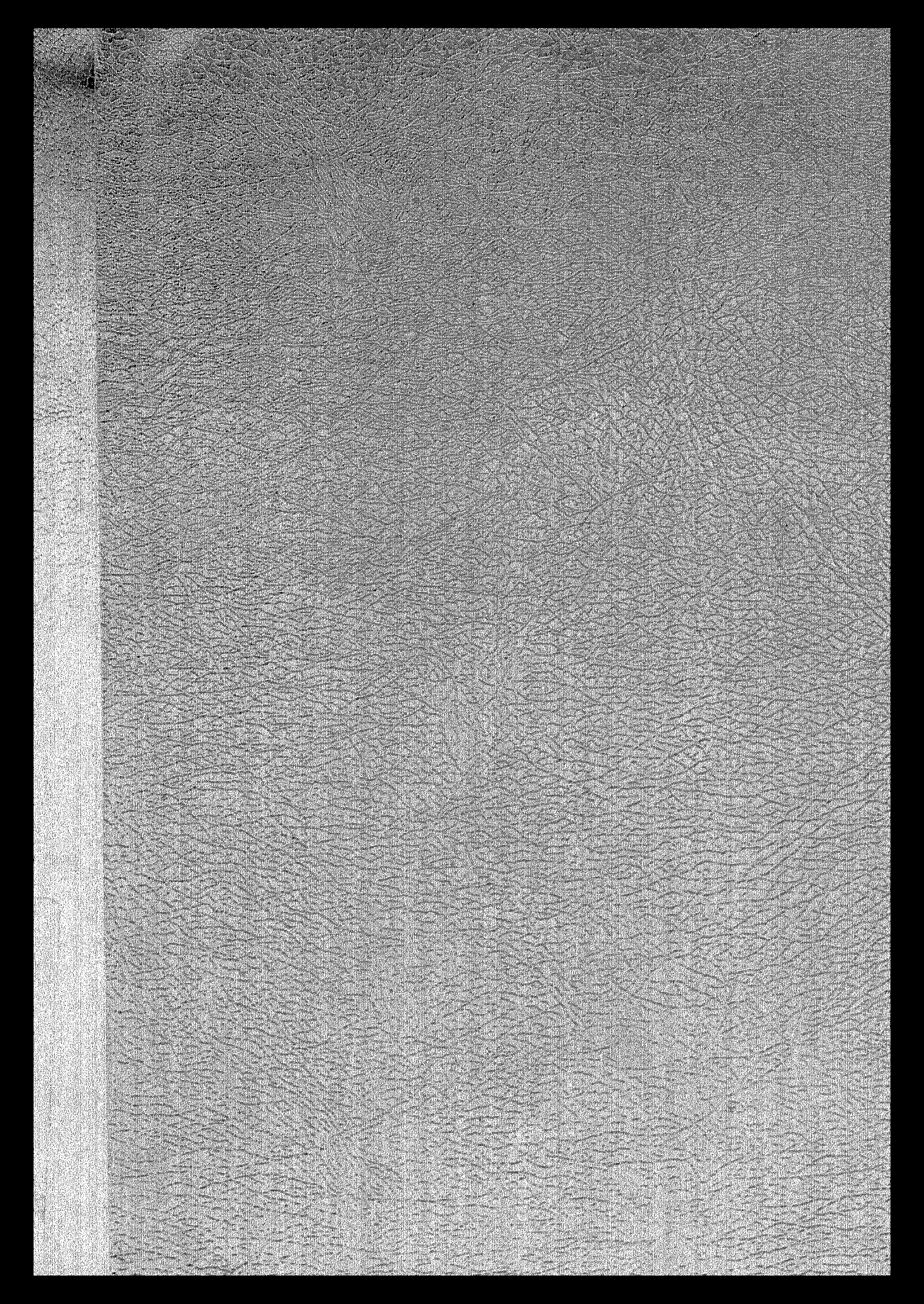


# POSSIBLE ROLE OF NITRIC OXIDE IN RENAL IMPAIRMENT IN PATIENTS WITH SPONTANEOUS BACTERIAL PERITONITIS

Thesis
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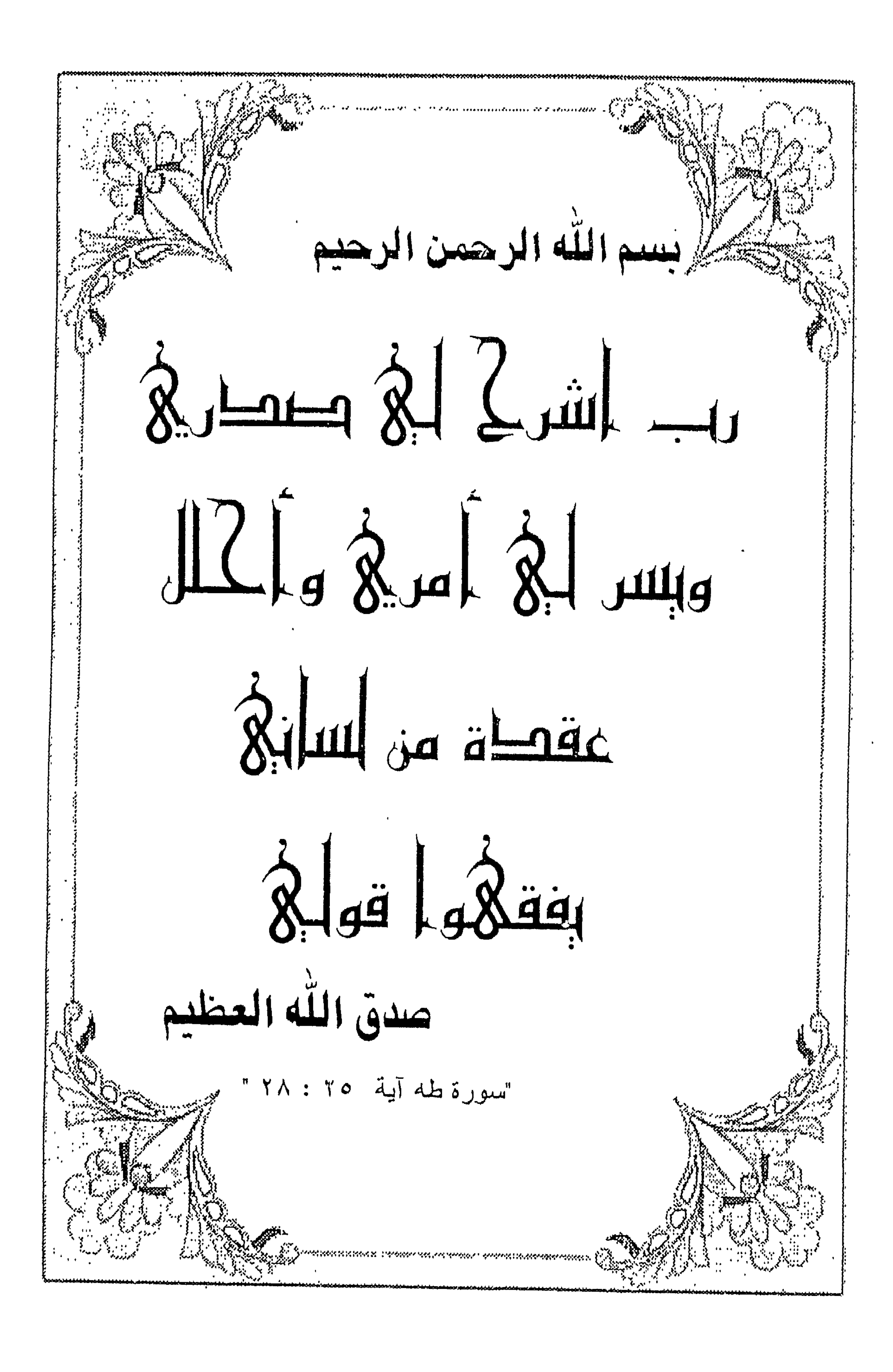

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بسم الله الرحمن الرحيم

# رب اشرح لي صدري

# ويسر لي أمري وأحلل

# عقدة من لساني

# يفقهوا قولي

صدق الله العظيم

"سورة طه آية ٢٥ : ٢٨"

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# CONTENTS

# LIST OF TABLES

# LIST OF FIGURES

# LIST OF GRAPHS

# LIST OF ABBREVIATIONS

| | |
|---|---|
| ADH | : Anti diuretic hormone |
| AFTP | : Ascitic fluid total protein |
| ALT | : Alanine transaminase |
| ANF | : Atrial natriuretic factor |
| ANP | : Atrial natriuretic peptide |
| AST | : Aspartate transaminase |
| ATN | : Acute tubular necrosis |
| AVP | : Arginine vasopressin |
| BP | : Blood pressure |
| BUN | : Blood urea nitrogen |
| Ca | : Calcium |
| cAMP | : Cyclic adenosine monophosphate |
| $CD_3$ | : Third component of clusters of differentiation |
| $CD_4$ | : Forth component of clusters of differentiation |
| CFI | : Chemotactic factor inactivator |
| cGMP | : Cyclic guanosine monophosphate |
| $CH_{100}$ | : Total hemolytic complement |
| CNNA | : Culture negative neutrocytic ascitis |
| CNOS | : Constitutive nitric oxide synthases |
| $CO_2$ | : Carbon dioxide |
| Cr. | : Creatinine |
| CT | : Computed tomography |
| $C_3$ | : Third component of complement |
| $C_4$ | : Forth component of complement |
| $C_5$ | : Fifth component of complement |
| D.BIL | : Direct bilirubin |
| E. coli | : Escherichia coli |
| EDRF | : Endothelium derived relaxing factor |
| ERSNA | : Efferent renal sympathetic nerve activity |

| | |
|---|---|
| ET | : Endothelin |
| Fe | : Iron |
| F. | : Female |
| GFR | : Glomerular filtration rate |
| GTP | : Guanosine triphosphate |
| Hb | : Hemoglobin |
| HRS | : Hepatorenal syndrome |
| HPV | : Hypoxic pulmonary vasoconstriction |
| IFN | : Interferon |
| Ig | : Imunoglobulin |
| IGIF | : Interferon gamma inducing factor |
| IL | : Interleukin |
| INOS | : Inducible nitric oxide synthase |
| JGA | : Juxta glomerular apparatus |
| K | : Potassium |
| LDH | : Lactate dehydrogenase |
| LDL | : Low density lipoprotein |
| LNAME | : N- nitrol- arginine methylester |
| LNMMA | : N-monomethyl-L-arginine |
| LPS | : Lipopolysaccharide |
| LTs | : Leukotrienes |
| M. | : Male |
| MNP | : Monomicrobial non-neutrocytic bacterascites |
| Na | : Sodium |
| NANC | : Non-adrenergic non-cholinergic |
| NE | : Norepinephrine |
| NMDA | : N-methyl-D-Aspartate |
| NMDAr | : N-methyl-D-Aspartate receptor |
| NO | : Nitric oxide |
| NOS | : Nitric oxide synthase |
| NOx | : Nitrite and nitrate |
| NP | : Natriuretic peptides |
| NSAIDs | : Nonsteroidal anti inflammatory drugs |
| O.A. | : Osteoarthritis |
| ONOO | : Preoxinitrite |

| | |
|---|---|
| PG | : Prostaglandin |
| PH | : Portal hypertension |
| PMN | : Polymorphnuclear |
| PT | : Prothrombin time |
| PVD | : Portal vein diameter |
| RAAS | : Renin- angiotensin-aldosterone system |
| RBF | : Renal blood flow |
| RES | : Reticulo-endothelial system |
| RNA | : Ribo-nucleic acid |
| RPF | : Renal plasma flow |
| RVR | : Renal vascular resistance |
| SAAG | : Serum-ascites albumin gradient+ |
| S. alb | : Serum albumin |
| SBP | : Spontaneous bacterial peritonitis |
| SD | : Standard deviation |
| SID | : Selective intestinal decontamination |
| SNS | : Sympathetic nervous system |
| T.BIL | : Total bilirubin |
| TGF | : Tubuloglomerular feedback mechanism |
| TIPS | : Transjacular intrahepatic portosystemic shunt |
| TNF-a | : Tissue necrosis factor-a |
| T.P. | : Total protein |
| TSB | : Tryptic soy broth |
| TX | : Thromboxane |
| URO | : Urodilatin |
| U/S | : Ultrasound |
| VEGF | : Vascular endothelial growth factor |
| VIP | : Vasoactive intestinal peptide |
| WBCs | : White blood cells |

# INTRODUCTION

# INTRODUCTION

Spontaneous bacterial peritonitis (SBP) is relatively common complication of patients with liver cirrhosis and ascites consisting of bacterial infection of ascitic fluid without any intrabdominal surgical cause of infection ***(Jiménez et al., 1999).***

SBP in cirrhotic patients lead to a long-lasting increased local production of nitric oxide (NO). This overproduction may contribute to the maintenance of splanchnic vasodilatation and thus worsen the hyperkinetic state in these patients ***(Bories et al., 1997)***.

In patients with cirrhosis and Spontaneous bacterial peritonitis, renal function frequently becomes impaired. This impairment is probably related to a reduction in effective arterial blood volume and is associated with a high mortality rate ***(Sort et al., 1999)***.

Hepatorenal syndrome (HRS) is a common complication of advanced cirrhosis characterized by renal impairment due to marked vasoconstriction of the renal vasculature and marked alterations in systemic haemodynamics ***(Gines, 2000).***

It has been suggested that serum nitrite and nitrate are highest in patients with functional renal failure (i.e. Hepatorenal syndrome) and that level correlate with the magnitude of endotoxemia which commonly associated with HRS ***(Epstein et al., 1997)***.

# AIM OF THE WORK

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The aim of this work is to estimate the serum and ascitic level of NO in patients with liver cirrhosis and ascites complicated with SBP with and without HRS, and in patients with HRS, and compare the results with patients with sterile ascites and with normal kidney function as a control group, to find out its possible relation to renal impairment.

# REVIEW OF LITERATURE

# ASCITES

## Introduction:

The term "ascites" is derived from the Greek word ***askos***, which means "bag" as in a distended bag ***(Gentilin et al., 1992).***

Ascites is a collection of extracellular fluid in the peritoneal cavity resulting from an imbalance between inflow and outflow through the peritoneal membrane. Ascites formation is not a static process, there is continuous movement of fluid and solutes into and out of the peritoneal cavity ***(Gines et al., 1987)***.

Ascites is a physical finding associated with certain specific diseases involving the liver, heart, kidney, peritoneum, thyroid gland, gonads and vascular or lymphatic system. Eighty percent of the cases of ascites are caused by hepatic disease, in the remaining 20% cancer, inflammation, renal, pancreatic or cardiac disease can be found ***(Ochs, 1995).***

## Causes of ascites *(Stephan et al., 1997)*:

**A-Portal hypertensive ascites:**

1- Liver cirrhosis.

2- Budd-Chiari syndrome.

3- Cardiac causes: congestive heart failure, Pericardial disease.

4-Veno-occlusive disease.

5- Portal vein thrombosis.

6- Polycystic liver disease.

7- Massive liver metastases.

**B-Non-portal hypertensive ascites:**

1- Malignant ascites.

2- Infectious ascites.

3- Nephrogenic ascites.

4- Pancreatic ascites.

5- Bile ascites.

6- Myxedematous ascites.

7- Chylous ascites.

## Factors contributing in ascites formation:

I- Portal hypertension.

II- Hypoalbuminaemia.

III- Renal function abnormalities;

A- Sodium retention.

B- Water retention.

C- Functional renal failure.

## I- Portal hypertension:

Ascites is a frequent complication of diseases causing sinusoidal portal hypertension e.g. Budd-Chiari syndrome, cirrhosis, veno-occlusive disease, constrictive pericarditis, right sided heart failure

and obstruction of the inferior vena cava, while it is uncommon in prehepatic portal hypertension. This phenomenon is thought to be due to differences in the anatomical and functional characteristics of the hepatic sinusoids and the splanchnic capillaries ***(Gragner & Barrowman 1984).*** Hepatic sinusoids are specialized capillaries that have a fenestrated endothelium and no basement membrane, therefore they are freely permeable to albumin, as indicated by the finding that protein concentration in hepatic lymph is approximately 95% of that of plasma.

Fluid exchange between the sinusoids and the hepatic interstitium is therefore only influenced by differences in hydrostatic pressure ***(LaVilla & Arroyo 1990).*** Thus in acute experimental obstruction to hepatic venous outflow, the increased pressure in the hepatic veins is almost completely transmitted back to the sinusoids, which results in marked increase in liver size due to passage of lymph from the sinusoidal lumen to the space of Disse ***(Greenway & Lautt 1970 and Laine et al. 1979). Laine et al., (1979)*** also claimed that for every mm. Mercury, elevation of sinusoidal pressure results in 60% increase in hepatic lymph production. Due to the low levels of compliance of the hepatic interstitium, lymph can accumulate without increasing interstitial pressure ***(Granger & Barrowman 1984).*** This results in 2 major consequences: (1) A striking increase in lymph flow through the liver and (2) the direct passage of lymph

from the lymph surface into the peritoneal cavity ***(Orioff et al., 1967 and Mitzner 1974).*** It is postulated by many experimental studies that this latter phenomenon could be an important mechanism of ascites formation ***(La Villa & Arroyo 1990)***

## II- Hypoalbuminaemia:

Hypoalbuminaemia in patients with cirrhosis is due to decreased hepatic synthesis, dilutional effects (due to salt and water retention), and a shift from intravascular to extravascular pools ***(Granger & Barrowman 1984).*** As noted earlier the hepatic sinusoids are normally freely permeable to plasma proteins. Thus, hydrostatic pressures in the hepatic sinusoids are the major determinant of fluid flux across the sinusoids, at least in early stages of the disease. As cirrhosis progresses, capillarization of the hepatic sinusoids occurs ***(Schaffner & Popper 1963).*** At this stage oncotic forces may be an important factor in determining net fluid flux across the sinusoids. Thus, lower serum albumin concentrations may contribute to ascites formation in patients with advanced cirrhosis. Lower serum albumin concentration may also contribute to fluid flux across the splanchnic capillary bed because these are not freely permeable to protein ***(Rocco & Ware 1986).***

# III- Renal function abnormalities:

## A- Sodium retention:

1- Role of renin - angiotensin - aldosterone system.

2- Role of Atrial natriuretic peptide (ANP).

3- Renal sympathetic nervous activity.

4- Role of kallikrein and Kinin system.

5- Vasoactive intestinal peptide.

It is the commonest and earliest renal abnormality in cirrhotic patients with ascites and it plays a critical role in the pathogenesis of ascites ***(Bernardi et al., 1993).*** This is proved clinically as: Ascites disappears in most of cirrhotics after inhibiting renal sodium retention with diuretics, despite portal hypertension and other splanchnic circulatory abnormalities remaining unchanged. Conversely diuretic withdrawal and or the administration of high sodium diet determine the reaccumulation of ascites in these patients ***(Arroyo et al., 1986).***

It is well established that sodium retention may occur in the setting of a normal glomerular filtration rate, indicating that the most important mechanism is an increased tubular sodium reabsorption. The factors that stimulate tubular reabsorption are not well known ***(Epstein et al., 1978).***

***Vasmonde (1988)*** considered the primary renal excretory abnormality causing fluid retention is a disturbance of sodium rather than water excretion. Many sodium retaining patients with ascites and edema are still capable of excreting large volumes of diluted urine when given excess amounts of water without sodium.

**1- Role of renin - angiotensin - aldosterone system:**

Plasma concentration of aldosterone, plasma renin activity and concentration and plasma concentration of angiotensin II were found to be normal in cirrhotics without ascites and increased in most patients with ascites. ***(Planes et al 1990 and Bernardi et al., 1994).***

***Perez & Oster (1993)*** found that administration of spironolactone a drug that antagonizes the effect of aldosterone on the renal tubules, increases sodium excretion in most of cirrhotic patients.

Although renin and aldosterone are metabolized by the liver it is clear that hyperreninemia and hyperaldosteronemia in cirrhosis with ascites are due to an increased secretion and not due to an impaired hepatic catabolism. ***(Bernardi et al., 1985).***

**2- Role of Atrial natriuretic peptide (ANP):**

ANP is one of the family of natriuretic peptides thought to play a role in alternation of sodium balance in advanced liver disease and ascites. Its level increases due to relative plasma expansion, and it is

associated with accompanying natriuresis. Attenuation of renal tubular response to ANP may be correlated to the degree of intrahepatic sinusoidal hypertension and associated reflex sympathetic nervous system (SNS) to the kidney. Actual tubular resistance to ANP may be due to reduced sodium delivery to the inner medullary collecting duct and/or increase degradation of cyclic guanosine monophosphate (cGMP) ***(Levy, 1997)***.

**3- Renal sympathetic nervous activity:**

***Nicholls et al. (1985) and Henriksen & Ring-Larsen (1994)*** postulated that increased sympathetic activity in cirrhotic patients with ascites may contribute to their impaired sodium and water excretion.

The increased efferent renal sympathetic nerves discharge will lead to increased release of norepinephrine (NE) by the kidney in patients with ascites ***(Dibona et al., 1988 and Henriksen & Ring-Larsen, 1994)***. Stimulation of renal sympathetic nervous activity increases renal tubular sodium reabsorption both by activation of the renin-angiotensin system and through proximal tubular mechanism ***(Persson et al., 1989)***.

The increased plasma NE concentration is due to an increased release and not due to an impaired degradation, since NE clearance is not significantly impaired in cirrhotics ***(La Villa & Arroyo 1990)***.

Some investigators have proposed that the increased plasma NE concentration in cirrhotics with ascites may not reflect a general activation of the sympathetic nervous system but that it may be a consequence of a selective activation of the renal sympathetic nervous activity. ***(Henriksen & Ring-Larsen, 1994)***.

**4- Role of kallikrein and Kinin system:**

Renin-angiotensin and Kallikrein-Kinin systems are two intrarenal hormone systems that interact at various levels and have directly opposite effect on vascular tone and sodium excretion. Kinins produce an increase in renal blood flow, urine flow and urinary sodium excretion. In cirrhotic patients suppression of the Kallikrein-Kinin system may contribute to renal vasoconstriction in cirrhosis ***(Scicli & Carrctcro, 1986)***.

**5- Role of vasoactive intestinal peptide (VIP):**

A vasoactive factor isolated from the small intestine has biological activity that mimics many of the associated circulatory and metabolic disorders of cirrhosis. Among these are peripheral vasodilatation, increased cardiac output, pulmonary shunting and hypotension. It may be increased due to decreased inactivation by the liver ***(Better & Schrier 1983)***.

**B- Water retention: Renal water handling in cirrhosis**

1- Decreased delivery of filtrate to diluting segment of the kidney.

2- Elevated level of antiduretic hormone (ADH).

3- Renal prostaglandins.

4- Increased sympathetic nervous system activity.

The cirrhotic patients develop an impaired renal ability to excrete free water ***(Arroyo et al., 1994 a).*** In most of patients with ascites free water clearance is reduced. When the renal ability to excrete free water is markedly impaired, patients become unable to eliminate excess ingested water and develop dilutional hyponatremia. However several possibilities have been proposed.

**1- Decreased delivery of filtrate to diluting segment of the kidney:**

According to ***Epstein & Norsk (1988)*** many decompensated cirrhotic patients manifested a decreased glomerular filtration rate (GFR). Further more, much evidence suggests avid reabsorption of filtrate along the proximal tubule ***(Chiandusi et al., 1978 and Epstein & Norsk, 1988).***

**2- Elevated level of antiduretic hormone (ADH):**

The most likely explanation for the hypersecretion of ADH in cirrhosis is a nonosmotic stimulation, because most patients have a degree of hyponatremia and hypo-osmolality that would suppress ADH release in normal subjects ***(Gines et al., 1998).***

Arterial vasodilatation characteristic of cirrhosis causes arterial underfilling leading to a baroreceptor mediated nonosmotic stimulation of ADH as well as activation of other antiduretic and vasopressor systems ***(Schrier et al., 1988).*** In the early stage of cirrhosis, this neurohormonal response is transient at the expense of an increase in plasma volume, and this stage is known as compensated cirrhosis. However, when the disease progresses, arterial vasodilatation increases and the neurohormonal response no longer compensates for the arterial underfilling. Vasoconstrictor systems are then constantly activated, thus leading to sodium and water retention, edema and ascites ***(Gines et al., 1998).***

Moreover, there is evidence that NO can stimulate central release of ADH and NO could therefore act through an indirect effect (baroreceptor-mediated) or a direct effect to activate a nonosmotic release of ADH ***(Gines et al., 1998).***

**3-Renal Prostaglandins:**

Several prostaglandins are synthesized in the kidney and although they are not primary regulators they modulate the effects of other factors and hormones locally. Prostaglandin $PGI_2$ and $PGE_2$ are vasodilators, and also increase sodium excretion through vasodilatation and a direct effect on the loop of Henle. They stimulate renin production and inhibit cyclic adenosine monophostate

(cAMP) synthesis, thereby interfering with the action of ADH. Thromboxane $A_2$ is a vasoconstrictor, reducing renal blood flow, glomerular filtration rate and perfusion pressure. $PGI_{2\alpha}$ is synthesized in the tubules and increases sodium and water excretion ***(Wong et al., 1993).***

Prostaglandins therefore have a significant role in sodium and water homeostasis. In conditions where there is a reduced circulating volume, which includes cirrhosis, there is increased prostaglandin synthesis. This counterbalances renal vasoconstriction by antagonizing the local effects of renin, angiotensin II, endothelin 1, vasopressin and catecholamines. The importance of this role is demonstrated clinically by the renal dysfunction seen in cirrhotics when non-steroidal anti-inflammatory agents are given. Without the vasodilatatory influence of prostaglandins renal blood flow and glomerular filtration rate fall because of unopposed vasoconstriction due to renin and other factors. Such an imbalance may be the trigger for the HRS ***(Wong et al., 1993).***

**4- Increased sympathetic nervous system activity:**

It is possible that an increase in efferent renal sympathetic nerve activity (ERSNA) also may contribute to the water clearance of cirrhosis. Several studies demonstrate a negative correlation between

peripheral plasma NE and the impairment of renal water excretion *(Bichet et al., 1982)*.

## Pathogenesis of ascites in liver cirrhosis:

**1- Diminished effective plasma volume (underfill theory):**

The term effective plasma refers to that part of the total circulating volume that is effective in stimulating volume receptors. Imbalance of starling forces develops in the hepatic sinusoids and splanchnic capillaries will lead to excessive lymph production exceeding the capacity of thoracic duct exceeds the capacity of the thoracic duct to return lymph to the systemic circulation, lymph accumulates in the hepatic interstitium and finally weeps from the surface of the liver into the peritoneal cavity ***(Better & Schrier, 1983).***

Ascites formation is theorized to result in a diminution of effective vascular volume, which in turn acts as an afferent stimulus to the renal tubule to increase sodium and water reabsorption. Thus according to the underfilling theory, renal sodium reabsorption is secondary to ascites formation and redistribution of plasma volume ***(Rocco & Ware 1986).***

**2- The overflow theory:**

According to this theory proposed by ***Libermann & Reynolds (1967)***, the initial event of ascites formation is a primary renal sodium retention (not due to a decrease in intravascular volume).

The initial stimulus for sodium retention may be due to reduced hepatic synthesis of a natriuretic agent, reduced hepatic clearance of sodium-retaining hormones or a hepato-renal reflex as a consequence of liver disease ***(Girgrah et al., 2000).***

**3- Peripheral arterial dilatation theory:**

It combines both the underfill and overfill views and it is based on the theory that the cirrhotic patient is in a state of peripheral arterial vasodilatation and microscopic arterio-venous fistulae are frequent. There is decreased filling of the arterial vascular tree with an increase in cardiac output and hormonal stimulation with rise in renin, aldosterone, NE and vasopressin. This leads to renal vasoconstriction and sodium and water retention which if severe and continued, the HRS results ***(Schrier et al., 1988)***.

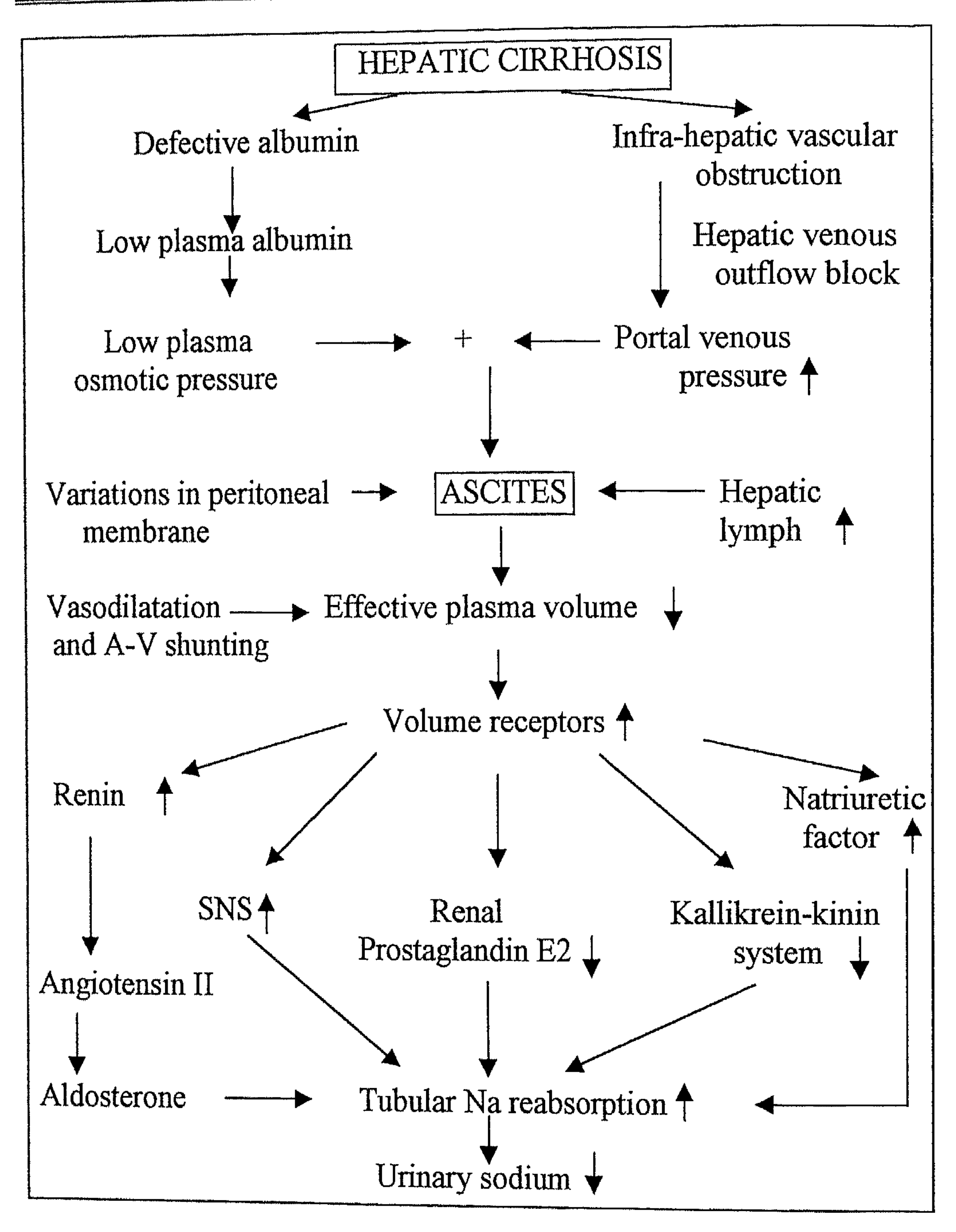



Fig. (1): The possible mechanisms of ascites formation in cirrhosis

***(Sherlock & Dooley, 1997)***

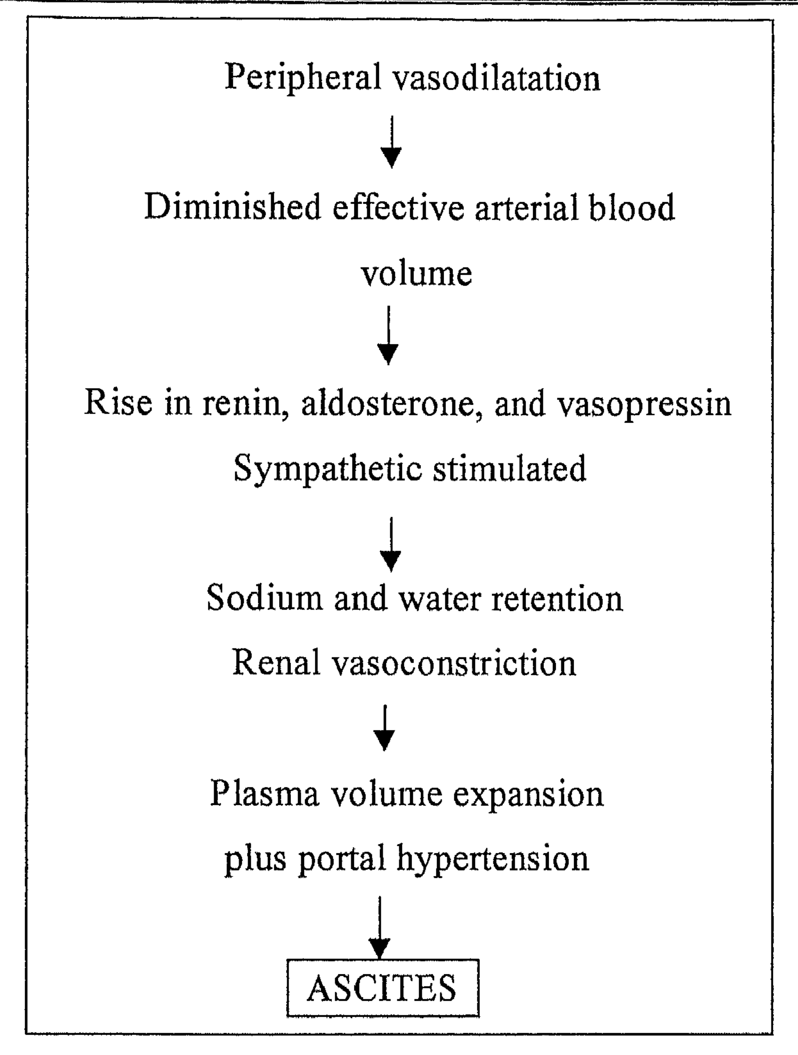



Fig (2): The peripheral arterial vasodilatation theory for ascites formation in cirrhosis

***(Sherlock & Dooley, 2002)***

## Circulation of ascites:

Once formed, ascitic fluid can exchange with blood through an enormous capillary bed under the visceral peritoneum. This plays a vital dynamic role, sometimes actively facilitating transfer of fluid

into the ascites and sometimes retarding it. Ascitic fluid is continuously circulating, about 50% of the fluid entering and leaving the peritoneal cavity every hour, there being a rapid transit in both directions. The constituents of the fluid are in dynamic equilibrium with those of the plasma ***(Sherlock & Dooley, 2002)***.

## Diagnosis of ascites:

The peritoneal cavity normally contains less than 50 ml of fluid. These patients usually are complaining of abdominal distension, bulging flanks, and positive shifting dullness ***(Runyon, 1995).***

**Diagnostic paracentesis:**

Abdominal paracentesis is one of the important procedures in evaluating the patient with ascites. The procedure should be performed in patients with newly onset ascites and when deterioration occurs in a patient with known ascites such as rapid accumulation of peritoneal fluid or refractory ascites, fever, abdominal pain, or worse encephalopathy is present. Such decompensation in patient with chronic liver disease could indicate supervening complication such as SBP, tuberculous peritonitis, hepatocellular carcinoma ***(Olafsson & Blei, 1995).***

The total and differential cell count, chemical profile: protein, albumin and lactate dehydrogenase (LDH), cytology and bacteriological examination (gram stain and bacterial culture) are the screening tests that are routinely performed on the initial specimen. ***(Runyon, 1995).***

**Cell count:**

The cell count is one of the most important ascitic fluid tests. An elevated ascitic fluid white blood cell count (WBC) count is seen in malignant diseases and all inflammatory processes ***(Olafsson & Blei, 1995).***

The mean WBC in uncomplicated cirrhotic ascites is 281 ± 25 cell/$mm^3$ and its upper limit has been reported to be 500 cell/$mm^3$ ***(Bar-Meir et al., 1979)***. However diuresis can concentrate ascitic fluid so that a WBCs count more than 1000 cell/$mm^3$ can be found in patients with cirrhosis and ascites. The upper limit of absolute polymorphnuclear leukocytic count (PMN) is usually stated to be 250 cell/$mm^3$ in uncomplicated cirrhotic ascitic fluid ***(Runyon, 1995).***

**Cytology:**

Cytology studies of ascitic fluid are appropriate whenever there is evidence of a malignant tumor, or when a non-malignant cause of

ascites is not obvious. A large volume of ascites (500 ml) is recommended for better results ***(Olafsson & Blei, 1995)***.

Although cytology is considered the "gold standard" in terms of diagnostic specificity (100%) and a positive cytology result confirms a malignant etiology in ascites, unfortunately it is not very sensitive with only 40-60% sensitivity in detecting malignant cells ***(Garrison et al., 1986 and Parsons et al., 1996).***

**Bacterial culture:**

The percentage of positive cultures can be markedly increased if ascitic fluid is inoculated directly into blood culture bottles at the bedside ***(Rimola et al., 2000).***

**LDH (lactate dehydrogenase):**

LDH enter ascitic fluid by diffusion from blood and by release from ascitic fluid white cells as they lyse ***(Runyon & Hoefs, 1985).*** The ascitic fluid level of LDH in uncomplicated cirrhotic ascites is usually less than half of the serum level ***(Runyon, 1995).*** Ascitic fluid LDH in SBP is frequently greater than the serum values, because of neutrophil release of LDH into the peritoneal cavity ***(Runyon, 1995)***.

**Serum ascites albumin gradient and ascitic fluid total proteins:**

Traditionally ascites has been classified as exudates if the ascitic fluid total protein (AFTP) was 2.5 gm/dl or more and as transudates if AFTP was less than 2.5 gm/dl. ***(Sampliner & Iber, 1974 and Cheson, 1985)***. This exudate-transudate concept was based on the assumption that fluid which is formed by "exudation" from an inflamed or tumorladen peritoneal surface (for example, bacterial peritonitis, tuberculous peritonitis...) is high in protein.

In contrast, the serum-ascites albumin gradient (SAAG) which defined as the serum albumin concentration minus the ascitic fluid albumin concentration ***(Runyon, 1995)***, has been proposed as a physiologically based alternative in the classification of ascites ***(Mauer & Manzione, 1988)***. This "gradient" has been shown to correlate directly with portal pressure, so that patients with gradients of 1.1 gm/dl or greater have been shown to have portal hypertension, whereas those with gradient less than 1.1 gm/dl do not have that disorder ***(Runyon, 1995)***.

***Terres et al. (1996)*** found that SAAG greater than $1.435 \pm 0.015$ gm/dl can be a signal for the presence of esophageal varices.

**Glucose:**

The glucose molecule is small enough to diffuse readily into body fluid cavities, therefore, the ascitic fluid glucose concentration

is similar to that of serum unless glucose is being consumed by ascitic fluid white cells or bacteria ***(Wilson et al., 1979).*** The ascitic fluid glucose in SBP that is detected early is similar to that of sterile fluid ***(Runyon & Hoefs, 1985).***

**Radiological features:**

Plain X-ray of the abdomen shows a diffuse ground-glass appearance. Distended loops of bowel simulate intestinal obstruction. Ultrasound and CT scans show a space around the liver and these can be used to demonstrate quite small amounts of fluid ***(Sherlock & Dooley, 2002).***

## Treatment of ascites in cirrhosis:

**1- Bed rest:**

Bed rest seems to enhance the effect of diuretics in patients with cirrhosis with ascites. Restriction of physical activity reduces metabolites that have to be handled by the liver ***(Sherlock & Dooley, 2002).***

In patients with cirrhosis and ascites, the assumption of the upright posture is associated with marked activation of renin-angiotensin and SNS and a reduction of glomerular filtration rate, sodium excretion and the natriuretic effect of furosemide ***(Ring-Larsen et al., 1986).***

**2- Sodium restriction:**

The amount of sodium retained in the body depends on the balance between the sodium ingested in the diet and the sodium excreted in the urine. As long as the sodium excreted is lower than that ingested, patients will accumulate ascites or edema. The reduction of sodium content in the diet to 40 to 60 mEq/day (1 to 1.5g of salt) causes a negative sodium balance and loss of ascites and edema in those patients with less marked sodium retention. In patients with moderate or marked sodium retention, such sodium restriction is not sufficient by itself to achieve a negative sodium balance, but it may slow the accumulation of fluid. These patients would require a more severe restriction of sodium (less than 20 mEq/day) ***(Gines et al., 1997).***

**3- Diuretic Therapy:**

The pharmacologic treatment of ascites has been based for many years in the administration of diuretics, drugs that increase urinary sodium excretion by reducing the tubular reabsorption of sodium.

Diuretic therapy in cirrhosis is based on the administration of spironolactone (50-400 mg/day), a drug that competes with aldosterone for the binding to the mineralocorticoid receptor in the collecting tubular epithelial cells, alone or in combination with some loop diuretics, especially furosemide (20-160 mg/day), that act by

inhibiting the Na-K-2C1- cotransporter in the loop of Henle ***(Gines et al., 1992).***

The response to diuretic therapy in cirrhotic patients should be evaluated by measuring body weight, urine volume, and sodium excretion regularly. An inadequate sodium restriction is a common cause of failure to diuretic therapy. This situation should be suspected when body weight and ascites do not decrease despite a high urine volume and natriuresis. Approximately 10% to 20% of patients with ascites either do not respond to diuretic therapy or develop diuretic-induced complications that prevent the use of higher doses of these drugs; this condition is known as refractory ascites ***(Arroyo et al., 1996).***

Common complications of diuretic therapy in patients with cirrhosis include electrolyte disturbances (hyponatremia, hypokalemia and hyperkalemia), hepatic encephalopathy, renal impairment, gynecomastia and muscle cramps ***(Gines et al., 1992).***

**4- Paracentesis:**

In the last 5 to 10 years therapeutic paracentesis has progressively replaced diuretics as the treatment of choice in the management of large ascites in patients with cirrhosis ***(Arroyo et al., 1994b).***

This change in treatment strategy is based on the results of several randomized comparative studies of paracentesis (either total removal of all ascitic fluid in a single tap or repeated taps of 4 - 6 liters/day) associated with plasma volume expansion and diuretics in cirrhotic patients with large ascites ***(Gines et al., 1987 and Quintero et al., 1995).***

***Esmat et al.,(2000)*** found that, paracentesis associated with intravenous administration of the cheap plasma expander as dextran has the same efficacy and as safe as albumin infusion in treating diuretic resistant ascites and preventing complications.

The results of many studies indicate that paracentesis is more rapid and effective, and is associated with less complications than conventional diuretic therapy. Because paracentesis does not modify the preexisting renal functional abnormalities of cirrhosis, patients should be given diuretics after paracentesis to avoid reformation of ascites ***(Ljubicic et al., 1994).***

**5- Other Therapeutic Methods:**

Peritoneovenous shunting was used frequently in the past in the treatment of ascites in cirrhosis, especially in patients with refractory ascites; however, its use has declined markedly due to both side effects (shunt occlusion, vena cava thrombosis, peritoneal

fibrosis) and introduction of alternative therapies, such as paracentesis ***(Arroyo et al., 1992).***

The main advantage of transjacular intrahepatic porto-systemic shunt (TIPS) over surgical shunts is the reduction of the operative mortality, and the main disadvantage is the frequent obstruction of the prosthesis, which results in increased portal pressure and reaccumulation of ascites. Potential problems of TIPS are the development of hepatic encephalopathy and impairment in liver function due to the shunting of blood from the liver to the systemic circulation. A recent comparative study in a small series of patients with refractory ascites showed an increased mortality in patients treated with TIPS, especially in those patients with poor liver function, compared with patients treated with paracentesis plus albumin ***(Lebrec et al., 1996).***

Liver transplantation has become a standard therapy for patients with end-stage cirrhosis, and the 5-year survival rate for adult patients submitted to liver transplantation is greater than 70%. Earlier recommendations suggested that the main indications for liver transplantation in patients with ascites were refractory ascites, recovery from spontaneous bacterial peritonitis and HRS; however, but, a significant proportion of patients do not reach the

transplantation because of the short survival expectancy associated with these conditions. ***(Llach et al., 1988 and Gines et al., 1997)***.

# SPONTANEOUS BACTERIAL PERITONITIS (SBP)

## Definition:

Spontaneous bacterial peritonitis (SBP) is a common and sever complication of cirrhotic patients with ascites characterized by infection of ascitic fluid without any intra-abdominal surgical source of infection ***(Navasa et al., 2000)***.

It occurs infrequently in patients with non-cirrhotic ascites, such as nephrogenic ascites ***(Krensky et al., 1982)***, and cardiogenic ascites ***(Pascual et al., 1988)***.

## History of SBP:

SBP has been recognized since at least turn of the century. Additional reports followed sporadically, but this disorder has been well characterized in the last 30 years, since Conn's series was published in 1971 ***(Conn et al., 1971)***.

SBP was defined by ***Jerome in (1986)*** as an acute onset of bacterial peritonitis without any evidence of rupture or contamination of the peritoneal cavity.

***Hallak (1989)*** also defined SBP as sudden onset of acute bacterial peritonitis without any apparent extra or intra-abdominal focus of infection in patients with ascites.

***Bhuva et al., (1994)***, defined SBP as an infection of the ascitic fluid in the absence of any obvious intra-abdominal source of infection.

## Prevalence of SBP:

SBP is a common and a potentially fatal complication of liver cirrhosis. Its prevalence in cirrhotic patients has been estimated to be between 8% and 27%, with a resulting mortality rate ranging from 48% to 57% ***(Pinzello et al., 1983).*** It accounts for 30% of all infections in cirrhotic patients ***(Wyke 1987 and Caly & Strauss, 1993).***

## Interpretation of ascitic fluid infection:

Two variants of neutrocytic ascites are found:

- Classical SBP (culture positive) which has been defined by:

1) An ascitic fluid PMN count greater than or equal to 250 cell/ml,
2) A positive ascitic fluid culture,
3) The lack of an obvious intra-abdominal source of infection. ***(Runyon and Hoefs, 1984b).***

- Culture negative neutrocytic ascites (CNNA) which has been defined by:

1) The presence of an ascitic fluid PMN count of greater than or equal to 500 cell/ml,
2) Negative ascitic fluid cultures,

3) Absence of an intra-abdominal source of infection,

4) No prior antibiotic treatment within 30 days ***(Bhuva et al., 1994).***

In a retrospective review by ***Runyon and Hoefs in (1984b)***, the characteristic of CNNA patients were compared with culture-positive patient. These data revealed that up to 35% of patient with SBP had CNNA. Analysis of clinical signs, symptoms, ascitic fluid measures, response to antibiotic therapy, and mortality rates showed no statistically significant differences between the two groups ***(Runyon and Hoefs, 1984b).***

Culture negative may represent a lack of sensitivity of certain methods or may represent the resolution phase of SBP in which host defenses have eradicated the organism without the help of antibiotic, but only elevation of ascitic fluid count ***(Runyon, 1988a).***

Another variant of SBP is monomicrobial non-neutrocytic bacterascites (MNB) in which the ascitic fluid cultures yield growth of bacteria (pure growth of a single type of organism), but ascitic fluid PMN count is less than 250 cell/ml. ***Runyon (1990)*** performed a prospective study in which 31.9 % of patient with culture-positive spontaneously infected ascites were found to have MNB. Fever was the indication for paracentesis in approximately half of the patient in both the SBP and MNB groups of patient. Abdominal pain was present in 50 % of patient with MNB. ***(Runyon, 1990).***

Secondary peritonitis can be defined when ascitic fluid total WBC count that exceeds 5000 cell/ml, with protein level greater than 2.5 g/dl indicates the presence of intra-abdominal source of infection ***(Runyon and Hoefs, 1984b).***

The presence of multiple organisms in ascitic fluid culture, presence of air under the diaphragm, the absence of a decrease in ascitic fluid PMN to less than the baseline tapping after 48 hours and persistence of positive culture help to differentiate patients with secondary peritonitis from those with spontaneous bacterial peritonitis. The importance of this distinction is that patient with secondary peritonitis need surgical intervention ***(Chu et al., 1994).***

Recently the term "community-acquired" and "hospital-acquired" (or nosocomial) have been applied to SBP ***(Navasa et al., 1996).***

SBP is said to be "community-acquired" if the initial ascitic sample reveals infection within 3 days of hospitalization, and "hospital-acquired" if SBP found more than 3 days after hospitalization ***(Novella et al., 1997).***

## Risk factors for ascitic fluid infection:

| |
|---|
| 1-Severe liver disease (Child-Pugh class C). |
| 2-Low total protein concentration in ascitic fluid (<1.5 gm/dL, especially if < 1.0 gm/dL). |
| 3-Esophageal variceal or gastrointestinal bleeding. |
| 4-Urinary tract infection. |
| 5-Intestinal bacterial overgrowth. |
| 6-Previous spontaneous bacterial peritonitis episode. |
| 7-Iatrogenic factors (e.g., urinary bladder and intravascular catheters). |

Table (1): Risk factors for ascitic fluid infection

***Hillebrand & Runyon (2000)***

**1-Severe liver disease (Child-Pugh class C):**

It is probably the main predisposing factor for developing SBP More than 70% of patients with SBP belong to class - C of Child-Pugh classification and the remainders are class B patients ***(Andreu et al., 1993 and Yoshida et al., 1993).***

**2-Low total protein concentration in ascitic fluid (<1.5 gm/dL, especially if < 1.0 gm/dL):**

The opsonic activity of the ascitic fluid is directly correlated to the ascitic fluid protein level in cirrhotic patients ***(Runyon et al.,***

***1985).*** The risk of developing the first episode of SBP was found to be high in cirrhotic patients with low ascitic fluid protein levels <1.0 g/dl ***(Guarner et at, 1999).***

**3-Esophageal variceal or gastrointestinal bleeding:**

***Deschenes & Villeneuve (1999)*** reported that patients with decompensated cirrhosis, who were hospitalized for gastrointestinal bleeding had a higher risk for developing bacterial infections during hospitalization, 32% of the studied cases developed SBP. This high incidence of bacterial infections could be due to several mechanisms such as depression of the activity of the reticuloendothelial system, alteration of intestinal permeability and an increase in bacterial translocation during the acute hemorrhage. Finally patients with gastrointestinal hemorrhage are subjected to a variety of invasive procedures for therapeutic and monitoring purposes ***(Deitch et al., 1990).***

**4-Urinary tract infection:**

***Ho et al., (1998)*** observed a high incidence of asymptomatic bacteruria in patients with community acquired SBP. He suggested that urinary tract infection could be a risk factor for the development of SBP in cirrhotic patients.

**5-Intestinal bacterial overgrowth:**

Intestinal bacterial overgrowth has been documented in patients with liver cirrhosis. It is suspected to play an important role in bacterial translocation in these patients ***(Chesta et al., 1991 and Casafont et al., 1995).***

**6- Previous spontaneous bacterial peritonitis episode:**

Patients with history of a previous episode of SBP have a high rate of SBP recurrence. ***Tito et al., (1988)*** observed that the probability of developing a new episode of SBP, in patients surviving an episode of SBP, was 69% in one year of follow up. Other authors have confirmed this high rate of SBP recurrence ***(Wang et al., 1991 and Andreu et al., 1993).***

**7-Iatrogenic factors (e.g., urinary bladder and intravascular catheters):**

Such as intravascular catheters and bladder catheters have also been proposed as favoring bacteraemia and SBP in cirrhotic patients ***(Carey et al., 1986).***

## Causative organisms:

The common causative organisms include Escherichia coli, Pneumococcus, Klebsiella and anaerobes ***(Friedman, 2000).***

## Route of infection:

### 1) Bacterial translocation:

Bacterial translocation is defined as the passage of viable bacteria from the gastrointestinal tract to lymph nodes, ***(Berg, 1992)***. The frequent finding of enteric bacteria producing SBP, in cirrhotic patients, suggests that these organisms originate from the intestine ***(Strauss &Boyer, 1996).***

### 2) Inoculation by haematogenous dissemination:

SBP may result from haematogenous seeding of the peritoneum. The simultaneous occurrence of meningococcal pneumonia and peritonitis illustrated this history ***(Hallak, 1989).***

### 3) Ascension through the female genital tract:

Vaginal infection was postulated to be a cause of SBP because of an apparent greater incidence of SBP in females ***(Mc Cartney, 1992).*** However, organisms isolated from the vagina correlated poorly with those isolated from the peritoneum in female patients with SBP ***(Clark, 1984).***

### 4) Lymphatic Spread:

Bacterial migration through lymphatic channels is commonly mentioned as a cause of SBP, although no direct evidence exists to support this route of spread ***(Clark, 1984).***

## Pathogenesis of SBP:

Three main factors have been implicated in the pathogenesis of spontaneous ascitic fluid infection:

I- Bacterial translocation from the gut to mesenteric lymph nodes ***(Runyon et at., 1994).***

II- Bacteremia secondary to impaired host immune-responsiveness ***(Mastuda et al., 1982).***

III- Decreased antibacterial activity of ascitic fluid ***(Runyon et al., 1985).***

Moreover, intra and extrahepatic shunting of portal blood, through portosystemic collaterals, contribute to the risk of infection by decreasing the clearance of bacteria ***(Hoefs, 1990).***

**I- Bacterial translocation:**

It has been shown that normally colonies in the gastrointestinal tract can cross the mucosa and infect the mesenteric lymph nodes, blood, spleen and liver, a process that has been termed bacterial translocation ***(Garcia-Tsao et al., 1995).***

The finding of enteric organisms in the mesenteric lymph nodes of experimental animals with portal hypertension and SBP has suggested translocation of intestinal organisms, from the lumen through the intestinal wall, to the ascitic fluid via lymphatics

***(Runyon et al., 1991; Garcia-Tsao et at, 1995 and Casafont et at., 1997).***

Increased bacterial translocation in cirrhotic patients is due to:

a) Increased permeability of intestinal mucosal barrier.

b) Intestinal bacterial overgrowth.

c) Decrease in host local immune defenses ***(Garcia-Tsao et al., 1993).***

**A) Increased permeability of intestinal mucosal barrier.**

Patients with liver cirrhosis have intestinal mucosal congestion and edema. Portal hypertension by producing structure changes in the bowel mucosa would favor bacterial translocation and lymphatic shunt in cirrhotic patients ***(Garcia-Tsao et al., 1993).***

**B) Intestinal bacterial overgrowth:**

In an experimental model of cirrhosis, ***Guarner et al., (1997)*** demonstrated that bacterial translocation of any organism was almost always associated with intestinal bacterial overgrowth of the same organism. These data suggested that bacterial overgrowth contributed to the development of SBP by promoting bacterial translocation.

**C) Decrease in host local immune defenses:**

Decreased reticuloendothelial phagocytic activity, deficient ascitic fluid opsonic activity and qualitative neutrophil dysfunction

have been reported in cirrhotic patients ***(Runyon, 1986, Rabinovitz, 1989, Runyon, 1993 and Bolognesi et al, 1994).***

## II- Bacteremia secondary to impaired host immune-responsiveness:

Impaired humoral immune mechanisms and defective reticuloendothelial system contribute to the greater risk of infections encountered in patients with liver cirrhosis ***(Deschenes & Villeneuve, 1999).***

### A) Impaired humoral immune mechanisms:

#### 1) Immunoglobulins:

Although serum immunoglobulins are usually present in normal or increased concentrations in patients with liver disease, impaired bactericidal function of IgM has been reported in 80 % of patients with cirrhosis ***(Rolando & Wyke, 1991).***

#### 2) Complement:

Complement factors are synthesized in the liver and tend to be reduced in proportion to the severity of the liver disease. Patients with fulminant hepatic failure have marked deficiencies of serum complement factors of the classical and alternative pathways, which cause severe defects of in vitro tests of opsonization and phagocytosis of E. coli by polymorphonuclear cells ***(Larcher et al., 1992).***

Complement deficiency also causes severe impairment of serum chemoattractant activity for polymorphonuclear cells ***(Wyke et al., 1993).***

***Mansour et al. (1997)*** found that the serum third component of complement system ($C_3$) level was significantly lower in patients with SBP than in those with sterile ascites. This reflected the inadequate hepatic synthesis of $C_3$, related to poor hepatic function, in patients with SBP.

**3) Chemoattractant activity:**

There is decrease in serum ability to stimulate the movement of normal polymorphs in acute and chronic liver disease ***(Yousif-Kadaru et al., 1984).***

***Maderazo et al., (1975)*** confirmed the presence of a chemotactic defect in cirrhotic patients and there was an increased level of a chemotactic factor inactivator (CFI).

Complement deficiency seems to be the prime reason of impaired chemotaxis in fulminant hepatic failure ***(Rajkovic et al., 1990).***

**4) Opsonization:**

Opsonins deficiency lead to defective coating of bacteria which become indigestible by polymorphs ***(Sherlock & Dooley, 2002).***

Macrophages and polymorphnuclear leukocytes are ineffective in phagocytosing bacteria in the absence of the specific and nonspecific opsonins such as complement fibronectin and immunoglobulins. Opsonization can be improved by transfusion of fresh plasma ***(Larcher et al., 1992).***

## B) Defective reticuloendothelial system:

Normally 90% of the reticuloendothelial system (RES) is localized within the liver and includes the Kupffer cells and other sinusoidal cells. The main function of this system and especially that of the hepatic (RES) is to phagocytose circulating bacteria. This is considered as the most important defensive mechanism against bacteremia. Spontaneous bacteremia is frequent in cirrhotic patients and correlates with poor removal of sulpher colloid by reticuloendothelial cells ***(Rimola et al., 1989)***.

The systemic clearance of substances removed by reticuloendothelial cells and by hepatocytes decreases in parallel with the severity of chronic liver disease ***(Hoefs et al., 1989).***

Reticuloendothelial phagocytic function shows severe impairment in most cases of fulminant hepatic failure and in 40% of cases of alcoholic liver disease ***(Wyke, 1987).***

The phagocytic activity of monocytes, the precursor elements of Kupffer cells, has been founded to be reduced in cirrhotic patients suggesting that a defective intrinsic phagocytic activity of RES cells may be present in these patients ***(Hassner et al., 1991)***.

The impaired Kupffer cell function is due to deficient plasma fibronectin, an opsonin for Kupffer cells in patients with liver cirrhosis ***(Naveau et al., 1990).***

**III- Decreased antibacterial activity of ascitic fluid:**

Some forms of ascites appear to be more susceptible to SBP than others .The ascites of patients with cirrhosis and children with nephrotic syndrome has been reported to be particularly susceptible, whereas ascites due to peritoneal carcinomatosis or heart failure seldom if becomes spontaneously infected ***(Runyon, 1988b).***

The understanding of the peritoneal defense mechanisms is necessary. First line defense appears to be the absorption of bacteria and particulate matter less than 10 um in diameter through the huge surface area of the peritoneum ***(Clark, 1994).*** Peritoneal fluid is drawn upwards into the transdiaphragmatic lymphatics and eventually into the thoracic duct by diaphragmatic motion. Bacteria can be recovered from the thoracic duct within minutes of an intraperitoneal injection ***(Simmons & Ahrenholz, 1981).***

Transdiaphragmatic removal of bacteria could be impaired when intestinal motility and respiratory efforts are decreased. Peritoneal contamination results in an immediate inflammatory response. Mast cell degranulation leads to vasodilatation, with exudation of plasma rich in antibodies and fibrinogen. Fibrinogen is converted to fibrin that traps bacteria resulting in decreased absorption of bacteria and probably endotoxins as well ***(Clark, 1994).***

Bacteria may be lysed by the activity of complement if they are serum-sensitive strains. However, most bacteria which cause serious infections including bacteremia, are serum-resistant and must be engulfed and killed by phagocytic cells. This process requires that the bacterial cell surface first be coated (opsonized) with IgG and / or the third component of complement .The fixation of complement to the bacterial surface is the most important step in opsonization ***(Runyon et al., 1989).***

Opsonic activity is defined as the in vitro ability of ascitic fluid to kill bacteria in the presence of normal neutrophils ***(Runyon, 1988a).*** The opsonic activity is directly related to the total proteins and the third component of complement of ascitic fluid ***(Runyon et al., 1985).*** Cirrhotic patients with low ascitic fluid opsonic activity have low $C_3$ and low total proteins (usually < 1 g/dl) in ascitic fluid

and are especially predisposed to develop SBP ***(Such et al., 1988, Rabinovitz et al., 1989 and Mansour et al., 1997).***

Patients with ascitic fluid proteins < 1 g/dl have been shown to have ten folds increase in their predisposition to SBP compared to patients with high protein ascites ***(Runyon, 1986)***. One fourth of patients with low protein ascites developed SBP, during a three years follow up, compared to only 4% of patients with higher levels ***(Llach et al., 1992).***

Fibronectin (FN) is a glycoprotein involved in the non-specific opsonization of a number of endogenous substances and bacteria ***(Doran et at., 1980 and Marquette et al., 1981).*** The ascitic fluid of cirrhotic patients displays, lower fibronectin concentrations when compared with that of non-cirrhotic patients ***(Prieto et al., 1986).***

***Mesquita et al., (1997)*** found that fibronectin in ascitic fluid was significantly correlated to $C_3$ and total protein concentrations. These data suggest that FN concentration in ascitic fluid is related to the opsonic capacity of this fluid, and that its concentration in the ascitic fluid may be a biochemical risk factor indicator for the development of SBP.

It has been postulated that the massive ascitis, which often occurs in cirrhotic patients, dilutes these components ***(Fromkes et al., 1987).***

Ascites that is deficient in antimicrobial properties is only the "fertile soil" in which SBP can develop. Bacteremia perhaps is the "seed" which results in SBP when it occurs in patients with susceptible ascitis ***(Runyon, 1988a).***

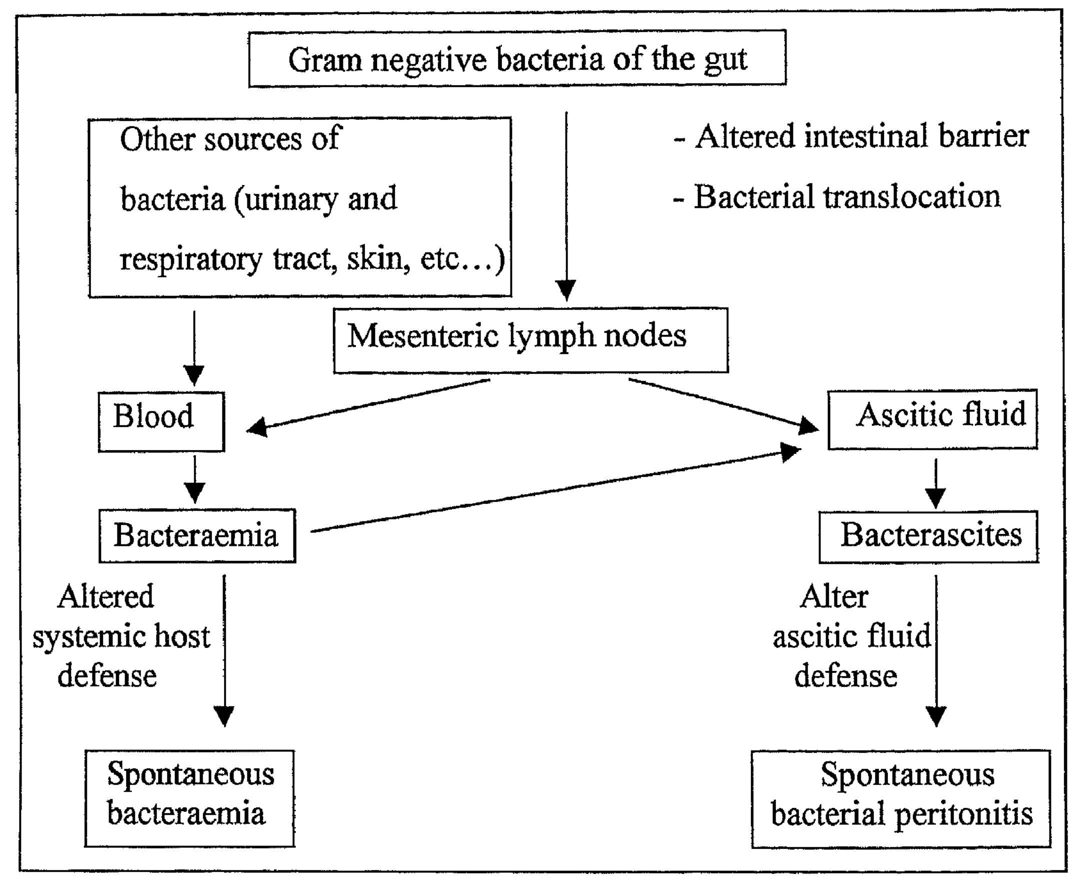



Fig. (3): Pathogenesis of spontaneous bacterial peritonitis

***(Guarner &Soriano, 1997)***

## Clinical presentation:

The clinical finding of SBP is variable, and a high index of suspicion is required for diagnosis ***(Arroyo et al., 1994a).***

The cardinal presenting features are fever and chills occur in up to two third of patients, abdominal pain in half of patients, and encephalopathy in one third ***(Liovet et al., 1997).***

Spontaneous bacterial peritonitis may present as classic peritonitis, with diffuse abdominal pain, fever, leukocytosis, hypotension and abdominal tenderness ***(Hillebrand & Runyon, 2000).***

However non-specific symptoms and signs such as hepatic encephalopathy, vomiting, diarrhea, gastrointestinal hemorrhage, shock or hypothermia may be present in high number of patients. Moreover, some patients initially show only a mild deterioration in mental status, progressive kidney failure or refractoriness to diuretic treatment. SBP can be totally asymptomatic ***(Hoefs et al., 1982 and Pintello et al., 1983).***

Instrumentation such as endoscopy in patients with variceal bleeding often proceeds SBP, although such instrumentation has been variably incriminated as a risk factor for SBP in epidemiological studies ***(Soriano et al., 1992 and Andreu et al., 1993).***

In patients with SBP, infection involvement of organs other than blood and ascites at the same time as SBP is relatively uncommon except with E. Coli. Pulmonary, pleural and urinary tract

infection with E. Coli have been reported simultaneously with SBP caused by E. Coli ***(Hoefs et al., 1982).***

Irrespective of the route of infections, the presence of bacteremia and spread of infection will be enhanced of the host defenses that are well recognized in patients with severe liver disease, these defects would be expected to result in frequent and prolonged infection ***(Mellencamp & preheim, 1992).***

## Diagnostic tests:

The diagnosis of ascitic fluid infection is based on clinical suspicion and ascitic fluid analysis. ***(Runyon, 1988b).***

A patient with a clinical assessment suggesting peritonitis should be evaluated with flat and upright abdominal radiographs, chest radiographs, complete blood count, serum amylase determination, urine analysis, blood and urine cultures ***(Clark, 1984).***

Performing a diagnostic paracentesis, even when there is minimal suspicion of infection is the key to achieve an early diagnosis of ascitic fluid infection ***(Runyon, 1988b).***

### Chemical analysis of ascitic fluid:

***Pinzello et al. (1986)*** found that the ascitic fluid PH was significantly lower (PH: 7.30) in patients with SBP than in sterile ascites (PH: 7.41). Moreover, since the PH levels of blood were not

different in the presence of infection, arterial-ascitic fluid PH gradient was significantly higher in SBP than in sterile ascites (0.12 versus 0.02).

Ascitic fluid LDH is released by disintegrating neutrophils and bacteria, So it is produced in a large quantity during SBP. Its concentration in the ascitic fluid increases if the PMN count rises high enough. A reduction in ascitic fluid lactate dehydrogenase concentration, is usually noted with recovery ***(Runyon & Hoefs, 1985).***

The total protein concentration in the ascitic fluid had been found to be lower in the SBP, and measurement of total protein concentration of ascitic fluid obtained on admission to the hospital is helpful in assessing the risk of development of SBP during the hospitalization. Patients who had an initial ascitic fluid protein concentration of $\leq$ 1g / dl were found to be 10 times more likely to develop SBP during hospitalization than those with an initial protein concentration > 1g /dl. This is explained by the absence of endogenous antimicrobial activity (opsonic activity) in ascitic fluid ***(Runyon et al., 1985).***

The opsonic activity was found to correlates very significantly with the total proteins, total hemolytic complement activity ($CH_{100}$), $C_3$ and $C_4$ concentrations in the fluid. The poor opsonic activity of

most cirrhotic ascitic fluid appears to be simply a reflection of the degree of dilution of antimicrobial proteins of the fluid ***(Runyon et al., 1985)***.

The albumin gradient provides very reliable information regarding the presence or absence of portal hypertension ***(Pare et al., 1983)***. Gradient greater than 1.1g / dl have correlated very closely with portal hypertension. Patients with portal hypertension appear to be at higher risk of developing SBP than non-portal hypertension related ascitic ***(Hoefs et al., 1982)***.

The glucose level in ascitic fluid in patients with SBP is decreased because of its consumption by stimulated neutrophil and bacteria ***(Akriviadis & Runyon, 1990)***.

**Bacteriological examination of the ascitic fluid:**

***Rimola et al., (2000)*** recommended that diagnosis of SBP must be based on the PMN cell count in ascitic fluid. A PMN count of more than 250 cells/$mm^3$ is highly suspicious of SBP and constitutes an indication for empirical initiation of an antibiotic treatment. An ascitic fluid polymorphnuclear leukocytic count of less than 250 cells/$mm^3$ exclude the diagnosis of SBP.

**Gram's stain:**

Gram's stain of ascitic fluid is usually negative in cirrhotic patients with SBP ***(Runyon et al., 1988).*** This is because the concentration of bacteria is usually very low (1 organism / ml or less). However, it may be helpful in identifying patients with gut perforation in whom multiple types of bacteria can be seen ***(Runyon & Hoefs, 1984a and Akriviadis & Runyon, 1990).***

Direct inoculation of ascitic fluid into agar plates provides a positive microbiologic diagnosis in less that 50 % of suspected cases of SBP. The inoculation of blood culture bottles with ascitic fluid has proven to be more sensitive for providing a micro- biologic diagnosis of SBP than direct plating methods (sensitivities 80 to 90 % compared with 50% respectively) ***(Castellote et al., 1990).*** .

Furthermore, it has been shown that the immediate or bedside inoculation of ascitic fluid into blood culture bottles produces better results than if blood culture bottles inoculated after transport of the specimen to the laboratory. Most of the blood culture bottles used either tryptic soy broth (TSB) or thioglycolate blood culture medium for inoculation. Techniques that concentrate microorganisms from ascitic fluid obtained from patients with SBP maximize their recovery ***(Hay et al., 1996).***

Ascitic fluid, blood and urine cultures should be obtained prior to antibiotic therapy in all patients suspected of having SBP. In many cases, ascitic fluid cultures are negative. Fortunately, blood cultures are positive in approximately 33 % of patients and provide antibiotic sensitivities. Urine cultures will also be positive in a large number of subjects and may indicate the source of bacteremia ***(Bhuva et al., 1994).***

## Treatment of active infection:

Patients with ascitic fluid neutrophil count > 250 cells / $mm^3$ and/or positive gram stain should be treated empirically with antibiotics .The choice of antibiotics depends on the organisms that is identified or suspected of being present. Empiric therapy requires the selection of antibiotics that will provide proper coverage for aerobic gram-negative organisms as well as gram-positive organisms as streptococci. Anaerobes are uncommon and do not need to be specifically covered ***(Hoefs et al., 1982).***

An aminoglycoside (i.e. gentamycin) and ampicillin would be seen ideal. However, the cirrhotic patients has a greater tendency to renal failure than does a normal patient and 30% of cirrhotic patients who are placed on gentamycin developed renal failure despite non toxic blood levels ***(Cabrera et al., 1982).***

Most organisms cultured are sensitive to chloramphenicol and this antibiotic has been used as the initial therapeutic agent for SBP. Since it is bacteriostatic for gram-negative organisms, fearing about recurrence of infection is possible and more common than anticipated. Furthermore, the cirrhotic patients appeared more susceptible to bone marrow suppression. Thus chloramphenicol is no longer recommended for testament of gram-negative cases ***(Hoefs et al., 1982).***

Aztreonam was studied as a treatment for SBP in 1986. Patients in the study received one gram every 8 hours for 14 days. All of these cases were culture proven gram negative infections. Within 3 days of initiating aztreonam therapy, patients became afebrile and their symptoms improved. In this study 3 of 16 patients developed gram positive superinfection ***(Ariza et al., 1986).***

The antibiotics of choice as initial empiric treatment for patients with SBP are third generation cephalosporins owing to their broad antibacterial spectrum, high efficacy, and safety. Cefotaxime is the drug most commonly used .In randomized comparative studies, cefotaxime has been shown to be more effective than other antibiotics such as aztreonam ***(Ariza et al., 1991)*** or aminoglucosides plus ampicillin ***(Felistar et al., 1985).***

Amoxicillin –clavulanic acid has also been shown to be effective as first-line therapy for SBP. One gram of amoxicillin with 0.2 gram of clavulanic acid given every 6 hours for 14 days achieved a cure rate of 85 % No side effects were reported with this therapy ***(Granger et al., 1990).***

Oral ofloxacin penetrates ascitic fluid relatively well. In highly selected patients with community-acquired SBP or CNNA in absence of azotemia, who have not been maintained on quinolone-based prophylaxis (which might indicate quinolone resistance), oral ofloxacin given for approximately 8 to 14 days is as effective as cefotaxime. ***(Novella et al., 1997).***

**Institution of broad spectrum antibiotics is recommended if:**

(1) The ascitic fluid PMN count is > 250 cells / $mm^3$ in a clinical setting of SBP,

(2) The ascitic fluid PMN count is > 500 cells / $mm^3$ regardless of the clinical picture or

(3) The clinical picture is typical of bacterial peritonitis regardless of ascitic fluid PMN count ***(Stassen et al., 1986 ).***

Recently, In patients with cirrhosis and SBP, treatment with intravenous albumin in addition to an antibiotic reduces the incidence of renal impairment and death in comparison with treatment with an antibiotic alone ***(Sort et al., 1999).***

## Follow up paracentesis:

The optimal time for repeat paracentesis after initiating antibiotic therapy is 48 hours. All patients will have ascitic fluid PMN count below the initial values. In addition, 95 % of the patients will have ascitic fluid culture negative when retapped after 48 hours. However, repeat paracentesis 48 hours after initiating therapy, demonstrating an ascitic fluid PMN count greater than the baseline value and / or the presence of continued positive ascitic fluid cultures, can help in identifying patients with secondary peritonitis ***(Akriviadis & Runyon, 1990).***

The magnitude of the decrease in ascitic fluid PMN counts after 48 hours correlated with the survival rate. The survivors had a mean drop of 92 % in ascitic fluid PMN count after 48 hours, whereas the non survivors had a decrease of only 66 % ***(Fong et al., 1989).***

## Duration of therapy:

Patients with SBP are typically treated empirically with parenteral antibiotics for 10 to 14 days. It has now been shown that a shorter course of antibiotic therapy is as effective as the longer course. Antibiotic therapy can safely be terminated once ascitic fluid PMN counts are less than or equal to 250cells/ ml with no apparent compromise in efficacy ***(Fong et al., 1989).***

***Runyon et al., (1991)*** had performed a prospective study to determine the optimal duration of therapy for SBP. All patients in the study were treated with 2 grams of cefotaxime every 8 hours. Ascitic fluid examination every 48 hours was done, until culture were sterile and ascitic PMN counts were less than or equal to 250 cells/ $mm^3$. The study demonstrated that short-course therapy of 5 days was as effective as long course 10 days therapy with no statistically significant differences as regards to infection related mortality, cure rates or recurrence rates. Thus cefotaxime given over a period of 5 days is both safe and cost effective.

## SBP and transplantation:

Transplantation appears to be relatively safe if it is performed after at least 4 day of intravenous antibiotic therapy that reduces the polymorphnuclear count and the treatment is continued after transplantation ***(Van Thiel et al., 1996).*** However, some investigators have reported increase mortality rates with transplantation following a recent bout of SBP ***(Ukah et al., 1993).***

## Prognosis:

Survival of hospitalized patients with SBP has increased during the past 15 years, from less than 40 % in early series to 70 % ***(Conn et al 1971)*** or even to 80% in recent studies ***(Navasa et al., 1996).***

Death is usually from multiorgan failure, accompanied by jaundice, encephalopathy and renal failure ***(Hoefs et al., 1982).***

Renal impairment may be irreversible HRS and is seen in about 30 % of patients; in one study, it was the single most important factor in predicting survival ***(Follo et al., 1994).***

The prognosis for patients who have recovered from a first episode of SBP is grave. It was found that the probability of recurrence is 43 % at 6 month, 69% at one year, and 74% at two years. The one year survival probability in this set of patients was 38 %. ***(Tito et al., 1988).***

## Primary prophylaxis:

***Runyon et al., (1992)*** have shown that in patient who have survived an episode of SBP, diuresis can be effective in increasing ascitic fluid opsonic activity. As mentioned before, patients with low protein concentration of the ascitic fluid and low ascitic fluid opsonic activity are predisposed to developing SBP. It has also been shown that patients with high protein concentration of the ascitic fluid and adequate ascitic fluid opsonic activity are seemingly protected from developing SBP. Diuresis decreases the amount of ascitic fluid, thereby increasing the concentration of protein and complement (opsonic) fractions in the remaining fluid, with subsequent lowering the incidence of occurrence of SBP ***(Runyon et al., 1992).***

Selective intestinal decontamination (SID) with oral non-absorbable antibiotics is an effective method in preventing SBP recurrence ***(Gines et al., 1990).***

The administration of oral norfloxacin 400 mg/day can cause the elimination of aerobic gram-negative bacilli from intestinal flora without affecting other microorganisms (by eliminating the aerobic gram-negative bacilli from the intestinal flora), the bacterial reservoir from which ascitic patients become infected is reduced. Although norfloxacin administration was effective in decreasing the probability of SBP recurrence, (20 % after one year), the number of hospitalizations, incidence of hepatic encephalopathy and survival rates is not changed ***(Gines et al., 1990).***

Patients with gastrointestinal hemorrhage or acute liver failure are at higher risk for developing bacterial infections. These infections can manifest themselves as bacteremia and / or SBP, pneumonia or urinary tract infections. Recent studies have shown that prophylaxis of these high-risk patients with antibiotics can greatly decrease the incidence of these infections ***(Soriano et al., 1992).***

The cost effectiveness of long term antibiotic prophylaxis has yet to be established, however, short term antibiotic prophylaxis has been shown to be effective in preventing SBP in high risk patients, such as

those with gastrointestinal hemorrhage or acute liver failure since they are less likely to survive an episode of SBP on admission to the hospital ***(Toledo et al., 1993).***

Despite the fact that these prophylactic measures have decreased the incidence of SBP recurrence, the probability of survival in these patients remains low. Thus, it is believed that all patients who have survived an episode of SBP be evaluated for liver transplantation, providing they are candidate for liver transplantation. Antibiotic prophylaxis can be considered for those patients who are candidates for liver transplantation. This intervention could help survival up to the time of transplantation ***(Bhuva et al., 1994).***

## Recurrence and secondary prophylaxis:

Recurrent infection occurs in 12 % of cases and may be higher if culture-negative neutrocytic ascites is included as a variant of SBP and 80 % of recurrent cases are due to E. coli ***(Crossley & Williams, 1985).***

In multivariate analysis, the only predictors of SBP recurrence were an ascitic fluid protein concentration of less than or equal to 1 gm/dl, prothrombin activity of less than or equal to 45% of normal and serum bilirubin > 4 gm /dl. This shows that patients with more severe liver disease, as identified by low prothrombin activity, low ascitic fluid protein concentration and high serum bilirubin, are at an

especially increased risk of developing SBP recurrence ***(Tito et al., 1988).***

Secondary prophylaxis with oral norfloxacin (400 mg/day) reduces the one- year relapse rate from nearly 70 % to 20 %; how ever, mortality and hospitalization rates appear unchanged ***(Gines et al., 1990).*** Side effects have been minimal, although the emergence of resistant organism may be become a problem ***(Dupeyron et al., 1994).*** In addition, expense and limited effectiveness, (in term of mortality and hospitalization) are of concern ***(Schubert et al., 1991).***

## Functional renal abnormalities in cirrhosis

***Epstein (1990)*** mentioned that the interrelationship of liver disease and simultaneous kidney Function had been recognized for hundreds of years. But unfortunately, liver-kidney interrelationship is exceedingly complex and at times is not fully appreciated.

The following table presents a frame work for considering those conditions that involve both the liver and the kidney for which relationships have been reasonably well defined.

**I. Disorders involving both the liver and the kidney:**

A. Systemic diseases involving both organs: amyloidosis, systemic vasculitis, sickle cell anemia, hemochromatosis, and Wilson's disease.

B. Toxins affecting both organs: carbon tetrachloride, methoxyflurane, and elemental phosphorus.

C. Infections involving both organs: leptospirosis, malaria, and human immunodeficiency virus.

D. Congenital or genetic disorders: polycystic disease.

E. Drugs: tetracycline and non steroidal anti-inflammatory drugs.

F. Pregnancy: pregnancy associated with hypertension and acute fatty liver.

**II. Primary disorders of the kidney with secondary hepatic involvement:**

A. Renal tumours without hepatic metastasis. Hepatic dysfunction associated with non-metastatic hypernephroma.

B. Renal tumours with extension to the liver or its vasculature.

**III. Primary disorders of the liver with secondary renal dysfunction:**

A. Extra hepatic biliary obstruction with secondary impairment of renal function.

B. Primary biliary cirrhosis.

C. Sclerosing cholangitis.

D. Hepatitis B and C.

E. Hepatorenal syndrome.

Table (2): Causes of liver dysfunction associated with renal abnormalities ***(Hoefs, 1995)***

## The Hepatorenal Syndrome (HRS)

### Definition:

Hepatorenal syndrome is a syndrome that occurs in patients with chronic liver disease and advanced hepatic failure and portal hypertension and also described with acute fulminate hepatic failure. It is characterized by unexplained renal dysfunction (impairment)

with marked abnormalities in the arterial circulation and activity of the endogenous vasoactive systems. It occurs in absence of significant abnormalities in kidney structures. The normalization of kidney function after liver transplantation confirms the functional origin of these disturbances of kidney function. A similar syndrome may also occur in the setting of acute liver failure ***(Arroyo et al., 1996).***

## Historical aspects:

The first detailed description of this syndrome was not made until ***(Hecker & Sherlock 1966)*** reported nine patients with liver disease associated with renal failure characterized by lack of proteinuria and very low urinary sodium excretion. These findings were subsequently confirmed in larger series of patients by several other groups. The functional nature of renal impairment associated with liver disease was further established by studies showing that the kidneys of these patients could be successfully transplanted to patients with chronic renal failure and that renal failure was reversible after liver transplantation ***(Koppel & Coburn, 1969 and Iwatsuki et al., 1973).***

## Types of HRS:

HRS may be classified on a clinical basis into two different clinical types:

(1) Type I hepatorenal syndrome:

Characterized by rapidly progressive reduction of renal function as defined by a doubling of the initial serum creatinine to a level greater than 2.5 mg/dl or a 50% reduction of the initial 24 hours creatinine clearance to a level lower than 20ml/min in less than 2 weeks.

(2) Type II hepatorenal syndrome:

In which the renal failure doesn't have a rapidly progressive course ***(Arroyo et al., 1996).***

## Pathogenesis of HRS:

The HRS is characterized by a progressive decrease in the renal blood flow and the GFR, avid sodium water retention with formation of ascites, azotemia and sometimes oliguria. HRS may be considered to be a slowly progressive, functional nephropathy, consequent on circulatory and dysregulatory collapse ***(Henriksen, 1995).***

The renal perfusion pressure is decreased due to multifactors, in the kidney, there is marked renal vasoconstriction that results in decrease glomeruler filtration rate. In the extrarenal circulation there is predominance of arteriolar vasodilatation, that results in reduction of total systemic vascular resistance and arterial hypotension ***(Arroyo et al., 1996).***

## Factors involved in pathogenesis of hepatorenal syndrome:

1-Heamodynamic change causing renal perfusion pressure.
2-Stimulation of sympathetic nervous system.
3-Increase synthesis of hormonal and renal vasoactive mediators.

### 1-Heamodynamic change causing decrease renal perfusion pressure:

The hyperdynamic circulatory state may be a reflection of a decreased in the "effective" plasma volume related to vasodilatation, which increases the vascular holding capacity, which also play a key role in the development of important complications of cirrhosis including ascites, edema, and HRS ***(Epstein, 1990).***

It is well established that severe liver disease is characterized by an increase in cardiac output and increases heart rate and decrease peripheral vascular resistance due to peripheral vasodilatation mainly in splanchnic circulation ***(Michielsen & Pelckmans 1994).***

### Splanchnic circulation:

Splanchnic vasodilatation is partly related to portal hypertension and the opening of portosystemic shunts and minor arteriovenous fistula, and portovenous shunts within the cirrhotic liver which have been recently described. This leads to activation of volume receptors that activate the rennin angiotensin system,

increased sympathetic outflow, and may increase release of atrial natriurentic factor and alter activity of kallikrein-kinin system ***(Bosch et al., 1998).*** These mediators increase renal sodium retention leading to ascites and edema and may alter renal blood flow leading to decrease glomeruler filtration and the HRS ***(Epstein, 1990).***

**Vasodilators:**

A number of vasodilators have been suggested as being active in decompensated cirrhosis. Among these are glucagon ***(Pizcueta et al., 1990),*** atrial natriuretic factor (ANF) ***(La Villa et al., 1990),*** NO ***(Moncada et al., 1991 and Mitchell et al., 1993 and Ros & Jiménez, 1995)*** and local mechanisms like the prostaglandins and the kinin-kallikrein system ***(Moore et al., 1991 and Wong et al., 1991).***

**Nitric Oxide:**

Among the vasodilator factors implicated in the hypothesis of peripheral vasodilatation is NO which is a potent vasodilator released in endothelial cells from L-arginine and acts by activation of guanylate cyclase ***(Lee et al., 1993)*** .It will be discussed in details later.

**Glucagon:**

Plasma glucagon levels are elevated in cirrhosis. Glucagon causes desensitization of the mesenteric circulation to catecholamines and angiotensin II, and causes vasodilatation at pharmacological

dose, also hyperglucagonism may account for 30-40% of splanchnic vasodilatation ***(Benoit et al., 1986).***

**Natriuretic hormones:**

The plasma concentration of major natriuretic hormones. Namely, atrial natriuretic peptide (ANP) and brain natriuretic peptide. It is increased in patients with cirrhosis and ascites. ***(Gines et al., 1988 and La Villa et al., 1992).*** These increased plasma levels are due to an enhanced cardiac release and not to a reduced systemic or hepatic clearance. Because natriuretic peptides have powerful effects on renal function and inhibit renin release. it is possible that increased natriuretic peptide levels may act as a homeostatic mechanism to counteract the effects of antinatriuretic and vasoconstrictor systems in the renal circulation ***(Angeli et al.,1994).***

**Prostaglandins:**

Prostaglandins are thought to participate in the pathogenesis of HRS. Their role has been proposed by ***Zipser et al., (1979)*** who showed that administration of PG synthetase inhibitor lead to reduction in the GFR and renal blood flow in cirrhotic patients. Moreover, administration of non-steroidal anti-inflammatory drugs in both ascitic and non-ascitis groups resulted in reduction of the GFR ***(Garella & Matarese 1984).***

Also, prostaglandins have peripheral vasodilating effect and thus cause systemic hypotension. PGE2 has a renal vasodilating action. The urinary excretion of PGE2 has been found to be markedly' decreased in patients with HRS. ***(Zipser et al., 1983).*** On the other hand, the urinary excretion of thromboxane B2 (TXB2) which is the metabolite of the potent vasoconstrictor thromboxane A2 has been reported to be markedly elevated in patients with HRS compared to those with chronic renal failure and healthy control. ***(Zipser et al, 1983).*** Thus it has been concluded that the imbalance between the vasodilating (PGE2) and the vasoconstricting (TXB2) metabolites of the arachidonic acid plays an important role in the pathogenesis of HRS ***(Zipser et al, 1983).***

Moreover, ***Fevery et al., (1990)*** reported temporary reversal of HRS in four patients after administration of misoprostol, which is a prostaglandin E1 analogue together with albumin.

**Endotoxins:**

Endotoxin (lipoplysaccharids produced by gastrointestinal bacteria) levels are usually elevated in patients who have decompensated liver disease and more in patients who have the hepatorenal syndrome. This is believed to be due to increased bacterial translocation and portosystemic shunting. Endotoxemia may cause peripheral vasodilatation mainly splanchnic vasodilatation,

possibly mediated by cytokines induction and increased NO synthesis *(Levy & Wexler, 1984).*

**Implications of vasodilatation:**

It's responses may be summarized as:

A- Activation of the renin-angiotensin-aldosterone system.

B- Increased vasopressin release.

C- Alternation in renal prostaglandin metabolism.

D- Activation of the sympathetic nervous system.

Although activation of these neurohormonal mechanisms are essential as homeostatic response to maintain arterial pressure within normal limits ***(Claria et al., 1991 and Schroeder et al., 1991).*** But some induce renal vasoconstriction, this is an important point since the renal vascular bed normally receives 25% of cardiac output, and is an important regulatory point of blood pressure control. So these mechanisms lead to altering the normal renal autoregulatory response, it also enhance water and sodium reabsorption all of these may contribute to the decreased renal blood flow which observed in HRS ***(Arroyo et al., 1994a and Vasmonde 1996).***

**A- Activation of the renin-angiotensin-aldosterone system:**

The renin-angiotensin-aldosterone system (RAAS) is stimulated in 50-80% of patients who have decompensated cirrhosis, and is further elevated in patients who have HRS. Increased levels of

angiotensin II protect renal function by selective vasoconstriction of the efferent glomerular arterioles. Although RBF may fall, GFR is preserved due to an increased filtration fraction. ***(Seller et al., 1981).***

In cirrhosis, inhibition of the RAAS by either saralasin or angiotensin converting enzyme inhibitors (e.g. captopril) causes marked hypotension and decreases GFR, whereas infusion of angiotensin II in cirrhosis has been shown to improve glomerular filtration in some patients, that because it may increase arterial pressure, and thus renal perfusion.This suggests that the integrity of the RAAS is important for the maintenance of renal function in cirrhotic patients, and that RAAS over activity doesn't contribute only to the adverse renal vasoconstriction ***(Henriksen, 1995).***

***Perez & Oster (1993)*** found that administration of spironolactone a drug that antagonizes the effect of aldosterone on the renal tubules, increases sodium excretion in most of cirrhotic patients.

**B- Increased vasopressin release:**

Antidiuretic hormone (ADH) or vasopressin levels are elevated due to several mechanisms. It has been proposed that enhanced ADH activity may be mediated by non-osmotic stimuli including decrease in peripheral resistance and arterial pressure. Also

decreased clearance may contribute to increase its activity ***(Bichet et al., 1982).***

However, ***Kim (1993)*** considered increased ADH levels are because of an increased hypothalamic synthesis and not because of a reduced systemic clearance.

There is significant increase in the plasma human atrial natriuretic factor in hepatorenal syndrome, At the same time, there is a significant increase in the renal arteries resistance, so the reason for renal vasoconstriction inspite of increased level of atrial natriuretic factor could be due to development of receptor insensitivity.***(Abdalla et al.,1997).***

Vasopressin causes vasoconstriction through V1-receptors and renal tubular water retention through V2-receptors in the medullary collecting ducts. This increases volume expansion by water retention, and helps to maintain arterial pressure. Vasopressin, however, causes splanchnic rather than renal vasoconstriction ***(Claria et al., 1991).***

**C- Alternation in renal prostaglandin metabolism:**

The overall action of Prostaglandins appeared to be that of promoting free water excretion. Most of the studies suggest that a relative diminution of renal prostaglandin may contribute to the anti diuresis of cirrhosis ***(Epstein et al., 1985, Raymond & Lifschitz, 1986 and Arroyo et al., 1994b).***

Fully established HRS, renal vasoconstriction appears to be independent of systemic haemodynamic. Absence of or decreased activity in local renal vasodilator systems, like the Prostaglandins, has been suggested to play a role in the HRS ***(Arroyo et al., 1983 and Moore et al., 1991).***

**2-Activation of the sympathetic nervous system:**

The SNS is highly activated in patients who have HRS. The elevation of plasma catecholamines in HRS is due to increased secretion, especially in renal and splanchnic vascular beds ***(Henriksen & Ring-larsen 1994).***

The sympathetic axis can be stimulated by three different mechanisms:

- Pressure receptors in response to hypotension in the aortic arch and carotid body, and volume receptors in response to hypovolemia in the atria.
- Non volume-dependent hepatic baroreceptors.
- Metabolic changes (e.g. secretion in response to hypoglycemia)

Activation of renal sympathetic nerves causes vasoconstriction of the afferent renal arterioles, with a decrease of renal plasma flow and GFR, and sodium retention. This also increases renin secretion and increased proximal tubular reabsorption of sodium resulting in further salt retention ***(Henriksen et al., 1988).***

Finally, activation of the sympathetic nervous system makes RBF more pressure-dependent, and α-adrenergic blockade induces arterial hypotension, impairing renal perfusion even further. In contrast, administration of NE usually results in improvement of renal function in HRS ***(Ring-Larsen, 1983 and Willet et al., 1985).***

Recent studies about the location and nature of the decreased systemic vascular resistance indirectly suggest that the main vascular bed responsible for arterial vasodilatation and reduced total peripheral vascular resistance in cirrhosis is the splanchnic circulation ***(Arroyo et al., 1996).***

***Epstein*** *(1997)* suggests that the imbalance between vasoconstrictor and vasodilator stimuli may contribute to the renal haemodynamic abnormalities that characterize the renal functional abnormalities of liver disease. As described before a number of vasodilators have been suggested to be active in decompensated cirrhosis, as glucagon, NO, ET-3, ANF, VIP, Substance P. prostaglandins, Encephalins and TNF. Nitric Oxide (its role will be discussed later) has been found to be responsible for the development of the splanchnic hyperemia, collateral circulation and portal hypertensive gastropathy. ***(Hartlep. et al., 1997).***

**3-Hormoral and renal vasoactive mediators:**

Many studies have now shown that there is increased synthesis of several vasoactive mediators such as endothelin, thromboxane A2, and arginine vasopressin (AVP).

**Endothelin:**

Increased plasma concentration of a potent vasoconstrictor, endothelin-l (ET l), have been described in patients with cirrhosis ***(Uchihara et al., 1992 and Gulberg et al., 1995).*** Specific receptors for this 21 -amino acid peptide are present in the myocardium, kidney, intestine, liver and other organs. This 21-amino acid peptide is a potent renal vasoconstrictor and a potent agonist of mesangial cell contraction, thus reduce the surface area available for glomerular filtration, renal perfusion, and urinary sodium and water excretion ***(Masoki & Yanagisowa, 1992 and Remuzzi & Benigini,1993).***

Most recent reports on ET-1 have shown increased circulating values in patients with decompensated cirrhosis **(Uchihara et al., 1992 and Moller et al., 1995).** A hepatosplanchnic generation of ET-1 has been identified in patients with cirrhosis and there is a direct relation between the hepatosplanchnic overflow of ET-1 and the circulating level of ET-1 on one hand and the portal pressure. Child score, and presence of ascites on the other **(Gulberg et al., 1995 and Moller et al., 1995).** The inverse correlation between circulating ET1

and markers of "the effective plasma volume" suggesting a role for this peptide in volume regulation **(Salo et al., 1997).**

***Moller et al., (1993)*** found highly increased plasma ET-1 in patients with the HRS and they described a net release of ET-1 from the kidney in this condition Although the endothelin have not yet been established as playing a role in decompensated liver cirrhosis, increasing evidence points towards a local role ***(Pinzam et al., 1992)*** and perhaps circulating endothelins are also implicated in the haemodynamic and homeostatic derangement of decompensated cirrhosis **(Gulberg et al., 1995 and Moller et al., 1995).**

**Cysteinyl leukotrienes:**

Leukotrienes (LTs) $C_4$ and $D_4$ are produced by inflammatory cells of the myeloid series, and their synthesis by the isolated kidney has been demonstrated. They are both potent renal vasoconstrictors, and cause contraction of mesangial cells. Their synthesis may be stimulated by endotoxemia, activation of complement, or various cytokines. There is good evidence that systemic, and probably renal synthesis of cysteinyl LTs are increased in HRS. Urinary LTE4 is markedly elevated, as well as N-acetyl LTE4 (probably a renal product of LT biosynthesis) in HRS ***(Laffi et al., 1997).***

**Arginine vasopressin:**

Among the vasoconstrictors, which is mentioned before, is arginine vasopressin (AVP) which is increased in decompansated cirrhosis. ***Pasqualetti & Casale, (1998)*** had studied 20 patients with HRS and concluded that, there is an increase of release of AVP in hepatorenal syndrome, due to the activation of the sympathetic adrenal system and to hyponatremia. AVP release occurs despite low plasma osmolality, which normally inhibits its secretion. This together with that of the atriopeptid-renin-angiotensin-aldosterone system could play an important role in promoting and/or in the maintenance of the hydro-electrolyte imbalance that characterizes the syndrome.

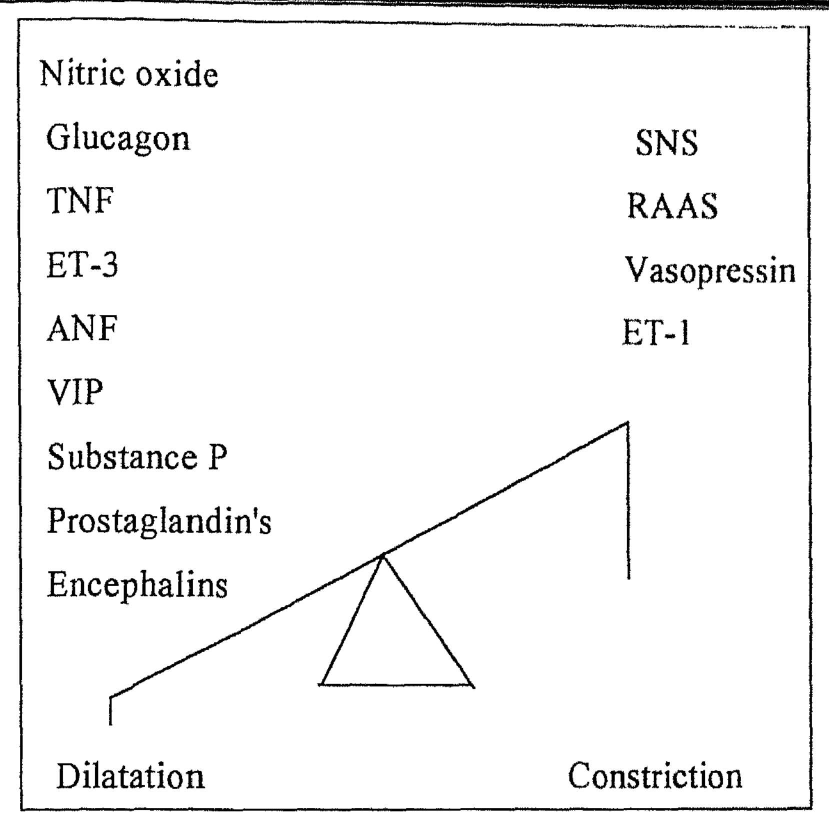



Fig (4): Imbalance between systemic vasodilator and vasoconstrictor system in decompensated cirrhosis. ***(Henriksen, 1995)***

## Pathology:

***Popper, (1983)*** Found that the kidneys of most of the patients dying with HRS were normal or showed minimal lesions as by light microscopy. There may be periglomerular, glomerular sclerosis, glomerular basement membrane thickening, mesangial matrix thickening or glomerular hypercellularity. By electron microscopy, there may be electron dense deposits in the capillary wall and mesangium. Thickening of the basement membrane, or the presence

of electron- dense esinophilic deposits in the mesangial matrix and in the subendothelial aspect of the basement membrane.

By immunofluorescence, there may be subendothelial and mesangial deposit of IgA and IgM or C3 ***(Eknoyan, 1983).*** In general, there is no correlation between these changes and renal dysfunction.

## Clinical Features:

Hepatorenal syndrome is the unique renal failure that develops in patients with cirrhosis, advanced liver failure, and severe sinusoidal portal hypertension. This renal failure is charactcterized by marked reduction of gomerular filtration rate because of renal vasoconstriction and is associated with severe sodium and water retention ***(Arroyo et al., 1996).***

In patients with cirrhosis, HRS may develop in two different clinical patterns ***(Rodese et al., 1975***). In some patient, there is an acute form (now termed type 1 HRS) which characterized by rapidly progressive reduction of glomerular filtration rate (GFR). With a marked rise in blood urea nitrogen (BUN) and serum creatinine levels, often associated with marked oliguria profound hyponatremia, and hyperkalemia. The patients are deeply jaundiced, ascites is often present for the first time or within few months. The prognosis of these patients is extremely poor ***(Gines & Escorselll, 1993).***

Frequently, progressive renal failure appears to be triggered by complications, especially bacterial infections, Gastrointestinal hemorrhage, major surgical procedures or acute alcoholic hepatitis. ***(Arroyo et al., 1996).***

In other patients there is a more chronic form (now termed type 2 HRS) which characterized by slowly progressive reduction of GFR with a moderate increase in BUN and serum creatinine levels that may persist for weeks or months. This type is preceded by chronic ascites associated with a mild elevation in serum bilirubin (less than 4mg/dl) level, hyponatremia, and mild decrease in creatinine clearance. The survival of these patients is significantly longer than that of the former group. ***(Arroyo et al., 1996).***

These two types of patients show similar qualitative abnormalities in the arterial circulation as well as activation of endogenous vasoconstrictor systems. However, the abnormalities are mcre marked in the former group of patients. It is therefore very likely that both types of renal failure represent distinct expressions of the same pathogenic mechanism that leads to a spectrum of renal disorder ranging from sodium retention to a rapidly progressive reduction of GFR ***(Arroyo et al., 1996).***

## Diagnostic criteria of HRS:

The international Ascites club proposed criteria for the diagnosis of the HRS in cirrhosis, some of these criteria are considered as major criteria and must be present for the diagnosis of HRS. The remaining criteria, most of them based on urinary indices, are not necessary for the diagnosis but may provide useful supportive evidence ***(Arroyo et al., 1996).***

**Major Criteria:**

- Chronic or acute liver disease with advanced hepatic failure and portal hypertension.
- Low glomerular filtration rate, as indicated by serum creatinine of > 1.5 mg/dl or 24 hour creatinine clearance < 40 ml/min
- Absence of shock, ongoing bacterial infection and current or recent treatment with nephrotoxic drugs. Absence of gastrointestinal fluid losses (repeated vomiting or intense diarrhea) or renal fluid losses (weight loss > 500 gm/d for several days in patients with ascites without peripheral edema or 1000 gm/d in patients with peripheral edema).
- No sustained improvement in renal function (decrease in serum creatinine to 1.5 mg/dl or less or increase in creatinine clearance to 40 ml/min or more) following diuretic withdrawal and expansion of plasma volume with 1.5 L of isotonic saline or plasma expander.

- Proteinuria < 500 mg/dl and no ultrasonographic evidence of obstructive or parenchymal renal disease.

**Additional criteria:**

- Urine volume < 500 ml/d.
- Urine Sodium < 10 m Eq/L
- Urine osmolality greater than plasma osmolality.
- Urine red blood cells < 50 per high powerfleld.
- Serum sodium concentration < 130 mEq/L.

Table (3): International Ascites Club's Diagnostic Criteria of HRS

*(Arroyo et al., 1996)*

## Differential Diagnosis of HRS:

Patients with cirrhosis are frequently exposed to a variety of clinical situations that may predispose to renal failure different from HRS. These conditions have to be excluded before the diagnosis of HRS is made. Gastrointestinal bleeding and bacterial infections are frequent complications of patients with cirrhosis that may lead to the development of shock (decrease in arterial pressure associated with reduction of tissue perfusion) that if prolonged, can cause acute renal failure because of acute tubular necrosis (ATN). The characteristics of ATN in these patients are similar to those of ATN in patients without liver disease. However, it should be taken into account that some patients with HRS may eventually develop ATN because of

intense renal vasoconstriction and subsequent renal ischaemia ***(Mandal et al., 1982).***

Recently, it has been shown that approximately one third of cirrhotic patients with SBP develop renal impairment in close chronological relationship with the onset of infection ***(Follo et al., 1994).*** The renal impairment is reversible in almost one third of cases after successful treatment with third generation cephalosporins. There fore, an ongoing bacterial infection should be excluded in cirrhotic patients with renal failure ***(Arroyo et al., 1996).***

Several drugs are known to induce renal failure in patients with cirrhosis, among them are NSAIDs ***(Boyer et al., 1979),*** aminoglycosides ***(Cabrera et al., 1982)*** and diuretics ***(Sherlock et al., 1966).*** NSAID'S have been reported to cause renal failure in patients with cirrhosis and ascites by inhibiting renal prostaglandin's synthesis. In addition, patients with cirrhosis are predisposed to develop ATN during treatment with aminoglycosides, particularly when these drugs are given in combination with cephalosporins. Finally, as stated before, the administration of inappropriately high doses of diuretics may lead to prerenal failure, especially in patients without peripheral edema ***(Shear et al., 1970 and Pockros & Reynolds,1986).***

| Factor | HRS | ATN | Pre-exiting renal disease |
|---|---|---|---|
| **Liver disease** | Advanced | Variable | Variable |
| **Ascites** | Present | Variable | Variable |
| **Encephalopathy** | Present | Variable | Variable |
| **Hypotension** | Late | Early | Not present |
| **Course** | Slow | Rapid | Slow |
| **Oliguria** | Late | Early | Variable |
| **Proteinuria** | < 0.5 gm/L | Present > 0.5 gm/L | Present > 0.5 gm/L |
| **Urine sediment** | Normal | Abnormal | Abnormal |
| **Urine/Plasma osmolality** | >1.2 | Low | Low |
| **Urine sodium** | <10mmoL/L | Moderate | Moderate |
| **GFR** | Low | Very low | Low |
| **Renal size** | Normal | Normal | Reduced |
| **Renal pathology** | None | Present | Present |

Table (4): Differential diagnosis of renal failure in cirrhosis

***(Sherman, 1997)***

Prerenal failure may also be found in patients with cirrhosis when there is depletion of intravascualr volume because of significant gastrointestinal fluid losses (repeated vomiting or intense diarrhea) or renal fluid losses because of aggressive diuretic therapy (Weight loss greater than 500 gm/ day for several days in patients

with ascites without peripheral edema or 1000 gm/d in patients with peripheral edema). This situation is characterized by reduced renal perfusion and low GFR and is rapidly reversible after restoration of intravascualr volume with plasma expanders.

By contrast, no significant changes in renal function are observed in patients with HRS after plasma volume expansion ***(Linas et al., 1986)*** to exclude any possible role of subtle reductions in plasma volume as cause of renal failure, renal function should be evaluated after diuretic withdrawal and expansion of plasma volume with 1.5 L of isotonic saline. If there is no sustained improvement in renal function (decrease in serum creatinine to 1.5 mg/dl or less or increase in creatinine clearance to 40ml/min or more) after this maneuver, the diagnosis of HRS is made ***(Arroyo et al., 1996).***

Only in the few cases in which there is a high index of clinical suspicion of intravascular volume depletion, renal function may be evaluated after normalizing central venous pressure or pulmonary capillary wedge pressure with plasma volume expansion ***(Arroyo et al., 1996).***

**In conclusion** iatrogenic renal failure in a cirrhotic patient must be diagnosed from genuine HRS as the prognosis is different and effective treatment is possible. The causes include, diuretics over dose, sepsis particularly spontaneous bacterial peritonitis and severe

diarrhea, NSAIDs reduce renal prostaglandin production, so reducing GFR and free water clearance ***(Garella & Matarese, 1984).***

## Prognosis of HRS:

The prognosis of HRS is poor with a mortality of about 50-95%, depending on the underlying etiology. Survival and recovery of renal function is generally dependent on improvement liver function due to recovery from the liver insult, effective hepatic regeneration or liver transplantation. Survival is therefore most commonly observed in those who have acute alcoholic hepatitis or acute liver failure, both of which may resolve spontaneously ***(Llach et al., 1988).***

Studies on the natural history of cirrhosis show constantly a close correlation between progressive renal dysfunction and poor prognosis.

| | |
|---|---|
| -Previous ascites | -Hyponatremia |
| -Absence of hepatomegaly | -Low urine sodium |
| -Poor nutritional status | -High plasma renin activity |
| -Low serum albumin | -High plasma aldosterone |
| -High serum bilirubin | -High plasma norepinephrine |
| -Increased serum creatinine | -Low arterial pressure |
| -Reduced water excretion | -Esophageal varices |

Table (5): Adverse prognostic factors in cirrhosis with ascites

***(Gines et al., 1997)***

## Management of HRS:

Renal function rarely recovers in the absence of hepatic recovery. The key goal in the management of these patients is to exclude reversible or treatable lesions which include infection, fluid and electrolyte disorders following vigorous treatment of ascites and gastrointestinal bleeding, and to support the patient until liver recovery (e.g. from alcoholic hepatitis), hepatic regeneration (acute liver disease) or liver transplantation. Many forms of treatment have been tried, but none is proven of value ***(Shearman, 1997).***

**I- General therapy:**

-Hepatic encephalopathy (avoid neomycin).

-Gastrointestinal bleeding.

-Infection.

**II- Minimize uremia :**

-Low-protein diet (<20gm/day).

-High carbohydrate intake (at least 200gm/day).

-Avoid nephrotoxic drugs.

**III- Increase renal excretory function:**

-Expand plasma volume, e.g. salt-free albumin.

-Diuretic therapy.

-Dopamine 1-2ug/Kg/min intravenously.

-Paracentesis.

**IV- Body fluids and electrolytes:**

-Water depletion.

-Hyponatremia.

-Hypokalemia.

-Hypomagnesium.

**V- Interventional therapy:**

-Le Veen shunt.

-TIPSS.

-Hemodialysis.

-Liver transplantation.

**VI- Other Therapies:**

-Ornipressin.

-Terlipressin.

-Midodrine and octreotide.

-Urodilatin.

-Antagonists of vasoactive substances.

-Antagonists of endothelin.

-Antagonists of Nitric oxide.

Table (6): Treatment of functional renal failure

***(Shearman, 1997)***

## Increase renal excretory function:

### a) Expand plasma volume:

In patients with cirrhosis and especially with SBP, renal function frequently becomes impaired. This impairment is probably related to vasodilatation, which cause a reduction in effective arterial blood volume with subsequent activation of vasoconstrictor systems, promoting renal vasoconstriction. The improvement in effective arterial blood volume would result in a reversal of HRS with suppression of the over activity of vasoconstrictors and increased renal perfusion (***Schrier et al., 1994***).

In patients with cirrhosis and SBP, treatment with intravenous albumin in addition to an antibiotic reduces the incidence of renal impairment and death in comparison with treatment with an antibiotic alone ***(Sort et al., 1999)***.

### b) Diuretic therapy:

Treatment of ascites consists of the administration of diuretics, drugs that increase urinary sodium excretion by reducing the reabsorption of sodium in the renal tubules. The diuretics most commonly used in patients with cirrhosis are spironolactone (50 to 400 mg/day given as a single dose because of its prolonged half-life), a drug that competes with aldosterone for the binding to the mineralocorticoid receptor in the collecting tubular epithelial cells,

alone or in combination with loop diuretics, especially furosemide (20 to 160 mg/day), that act by inhibiting the (Na-K- 2Cl) cotransporter in the loop of Henle. The response to diuretics in cirrhotic patients should be evaluated by measuring body weight, urine volume, and sodium excretion regularly ***(Gines et al., 1992)***

Vigorous treatment of ascites with high dose of diuretics may cause fluid and electrolyte disorders which may impair hepatic function and hence kidney function. However, if volume depletion is corrected as well as electrolyte disorders, combined therapy of Dopamine l-2ug/kg/min along with frusemide or bumetanide may improve urine output. ***(Shearman, 1997).***

**c) Dopamine:**

Dopamine is endogenous catecholamines that exert selective renal and mesenteric vasodilatation at doses of 1-3 ug/kg/min via dopaminergic-receptor stimulation, resulting in improved blood flow and urine output. Positive inotropic effect at a dose of 2-8 ug/kg/min. due to B1-adrenergic receptor stimulation. At doses of 7-10ug/kg/min alpha-adrenergic receptor stimulation predominates ***(Sal et al., 1996).***

***Carcoana (1996)*** concluded that, dopamine has the unique ability, compared with other catecholamines, to improve renal blood flow, GFR, sodium excretion and creatinine clearance. A therapeutic

renal effect of combined low dose dopamine with furosemide or prostaglandin results in enhanced renal effects in HRS.

## Body fluid and electrolytes:

### a) Water depletion:

Occasionally, a patient can become sodium and water depleted due to fluid loss by vomiting, diarrhea, paracentesis or vigorous diuretic therapy, in which case replacement therapy may lead to a marked improvement in renal and hepatic function ***(Galambos & Wilkinson 1962).***

### b) Hyponatremia:

As mentioned before, patient may occasionally become depleted from sodium and water but more commonly patients are over hydrated, as evidenced by ascites and edema and they often have a dilutional hyponatremia that may require the following management ***(Shearman, 1997).***

- **Mild hyponatremia: (124-130 mmol/L)**

Doesn't require treatment if the serum sodium is stable and an increased sodium intake should not be allowed, as patients with ascites always have a high total body sodium (normal 130-135 mmol/kg body weight).

- **Moderate hyponatremia: (115-124 mmol/L)**

Is not a serious sign if the patient isn't uremic and there are no other electrolyte abnormalities, restriction of water intake (0.5-1.0 L/day) is all that is required.

- **Sever hyponatremia: (<115 mmol/L)**

Occurs occasionally and results from a combination of excessive water intake and a limited free water clearance due to increased ADH production. Since hyponatremia in ascites usually develops over a period of time, a certain adaptation of the brain takes place and even very low serum sodium concentrations in the patients are rarely accompanied by symptoms. However, when symptoms do occur, hyponatremic encephalopathy may be difficult or impossible to distinguish from hepatic encephalopathy and in such cases hyponatremia should be treated.

- **Asymptomatic or less severe symptoms:**

Such as anorexia, nausea and headache and serum sodium> 110 mmol/L treated with water restriction up to 500 ml/day. IF treatment is unsuccessful or if patients are not compliant, slow correction of the serum sodium combined with paracentesis and an albumin infusion may be tried ***(Shearman, 1997).***

- **In patients with more severe symptoms:**

Such as vomiting, confusion, ataxia, fit and who are at risk of respiratory arrest, more aggressive treatment is obligatory. The objective is to reduce brain edema by increasing gradually sodium concentration in intensive care unit, where patient is monitored and intubated if respiratory insufficiency occurred. The target is to increase serum sodium to 130 mmol/L slowly with a maximum increase of 25 mmol/L over 24-48 hours. This is achieved by constant infusion of hypertonic sodium chloride ***(Arieff, 1993).***

**c) Hypokalemia:**

Potassium depletion may be present in these patients inspite of uremia. The plasma potassium concentration doesn't reflect the total body potassium but it is the best available guide to therapy; hypokalemia affects renal function adversely and worsens encephalopathy when potassium level is below 3.5 mmol/L treatment should be started. Some patients have marked potassium deficiency, so large amounts of I.V. potassium may be required but rate of infusion not exceeding 25 mmol/h and in concentrations not exceeding 40 mmol/L, with frequent checks of serum K ***(Shearman, 1997).***

**d) Hypomagnesium:**

Its deficiency may account for an inability to correct hypokalemia. Magnesium may be given as magnesium chloride at a rate between 25-100 mmol/day depending on the plasma magnesium concentration **(Lim & Jacob 1972).**

## Interventional therapy:

### 1. Le Veen Shunt:

Peritoneovenous shunts were developed by ***(Le Veen et al., 1976)*** to drain ascites from the peritoneum directly into the systemic circulation via the superior vena cava. Peritoneovenous shunts have been advocated for the hepatorenal syndrome but evidence is lacking that this syndrome can be reversed, A Peritoneovenous shunt is a prolongation, of misery for most patients ***(Shearman, 1997).***

### 2. TIPS:

The transjugular intrahepatic portosystemic shunt (TIPS) has been introduced recently in clinical practice for the management of cirrhotic patients with variceal bleeding. ***(Rossle et al., 1994 and Shiffman et al., 1995).*** A number of studies have also shown that the reduction of portal pressure induced by TIPS is associated with beneficial effects on renal function.

***Guevara et al., (1998)*** had studied that TIPS improves renal function and reduces the activity of vasoconstrictor system in

cirrhotic patients with HRS. Therefore, TIPS could be beneficial in the management of severe clinical condition. However small number of patients and lacking of control group make definitive conclusions about the efficacy and safety of TIPS in the management of HRS type 1 can't be obtained.

**3- Portocaval Shunt:**

Portocaval shunts can relieve functional renal failure in cirrhosis ***(Schroeder et al., 1970),*** but hardly any of the patients are fit for surgery.

**4- Hemodialysis:**

Hemodialysis or peritoneal dialysis are of limited value and may be complicated by gastrointestinal bleeding or hypotension ***(Perez & Oster 1978).*** However, some reports suggests that intermittent or continuous venovenous hemofiltration is a well tolerated and safer therapy allowing recovery of hepatic and renal function after an a acute insult ***(Shearman, 1997).***

**5- Liver transplantation:**

Classical indications for liver transplantation in patients with ascites with existence of refractory ascites, hyponatremia, recovery from spontaneous bacterial peritonitis, and development of HRS. However, with these guidelines a significant proportion of patients do not reach transplantation because of the short survival expectancy

associated with these conditions (survival time less than 6 months) ***(Bataller et al., 1998).***

**Other Therapies:**

**1. Ornipressin:**

***Guevara (1998)*** had studied that the administration of systemic vasoconstrictors, particularly Ornipressin (a synthetic derivative of vasopressin, a potent vasoconstrictor agent with a weaker antidiuretic action), and combined with plasma volume expansion with albumin for a prolonged period of time (up to 2 weeks) may improve markedly renal function in patients with HRS. However, this therapy may be associated with ischemic complication.

**2. Midodrine:**

The long term administration of Midodrine (an alpha-adrenergic agonist) in combination with octreotide parentrally in conjunction with infusion of 50-100 ml of 20% human albumin solution for 20 days seems to be an effective and safe treatment of type 1 HRS in patients with cirrhosis ***(Angeli et al., 1999).***

**3-Urodilatin (URO):**

A renal natriuretic peptide type A. known as Urodilatin derived from the gene of Natriuretic peptides (NP) type A, a message for the prehormone is transcribed in heart and kidney physiologically. URO binds to; luminal receptors (NPR-A) in the collecting duct resulting

in a cGMP-dependent signal transudation. That is followed by an interaction with the amiloride-sensitive sodium channel, which induces diuresis and natriuresis. Preliminary results from recent studies indicate that URO may be effective in patients suffering from hepatorenal syndrome ***(Meyer et al., 1998).***

**4-Antagonists of Vasoactive Substances:**

a) Antagonist of endothelin-1.

b) Antagonist of Nitric oxide (It will be discussed later).

**a) Antagonist of endothelin-1:**

Three patients with HRS were selected for treatment with a short infusion of BQ 123, a cyclical peptide endothelin-1 receptor antagonist, After baseline measurements, consecutive 10, 15, 100 nmol/min BQ 123 infusions were given for 60 min each, via a central vein. GFR improved and showed a dose response relation to BQ 123. No changes in heart rate or mean arterial pressure were detected, or in systemic vascular resistance, or in cardiac output. Therapeutic trials of prolonged infusions of non-peptide endothelin antagonists appear justified ***(Charles et al., 1996).***

## Conclusion:

HRS is a terminal event that is unresponsive to therapy. However, the iatrogenic form of the syndrome could be prevented by avoiding over duiresis and nephrotoxic drugs. Ascites should be

slowly treated. Electrolyte disturbance should be recognized and corrected. The management of the condition is conservative. Many forms of treatment have been tried. However, any improvement is very temporary and liver transplantation stills the only effective treatment of this lethal syndrome ***(Punukollu & Goplasmamy, 1990).***

# NITRIC OXIDE

## Introduction:

The discovery of an endothelium-derived relaxing factor (EDRF) is reported by ***Furchgott & Zawadski in 1980.*** In 1986, several investigators independently proposed that EDRF was NO, or NO containing substance, based on their observations of its similarity to other nitrovasodilators in its biological and physical properties. ***Ignarro et al., (1987)*** subsequently, ***Palmer et al., (1988)*** used chemiliuminescence and bioassay techniques to provide definitive evidence that NO was synthesized by endothelial cells and was responsible for the relaxing activity of EDRF.

NO is a gaseous biological messenger molecule that has been found to play a fundamental regulatory role in the body. It is involved in cardiovascular, immune, reproductive and digestive physiology and its presence in the brain indicates that it has a neuronal function. Several areas of research suggest that low level or absence of NO may be the underlying cause of some forms of essential hypertension and impotence while overproduction could be the cause of neuronal damage, septic shock, and immune related tissue damage ***(Patel, 1994).***

During the last 5-6 years a series of discovery from many different centers of research came together revealing the major

biological roles of NO as a neurotransmitter in the nervous system and other parts of the body. It is a potent vasodilator and a cytoprotective substance. In the digestive tract, it is extensively distributed from the mouth down to the anus when it is involved in splanchnic and systemic haemodynamics, in mucosal protection and it is acting as an inhibitory non-adrenergic non-cholenergic neurotransmitter and relaxant of smooth musculature ***(Vanderwinden, 1999).***

## Reactivity of NO:

NO is a gaseous free radical, is labile (half life < 15 seconds) it is slightly soluble in water. In dilute solution NO has half life of < 10 seconds because of rapid oxidation to inorganic nitrite and nitrate ***(Rubanyi & Van Houtte, 1986).*** NO has properties that make it unlike any known biologic mediator. NO is very lipophilic and can readily permeate biologic membranes ***(Ignarro, 1989).***

The chemistry of NO however involves interrelated radox forms, the most important reactions are believed to be these with oxygen, with transitional metal ions and with free thiol ***(Stamler et al., 1992)***. NO bind to oxyhemoglobin and other heme-containing proteins, its biologic actions are rapidly terminated by binding to oxyhemoglobin ***(Palmer et al., 1987)***.

NO reacts with superoxide anion to yield peroxynitrite which can rearrange into nitrate in reaction and produce the toxic hydroxyl radical ***(Pryor & Squadrito, 1995)***, or promote oxidative injury via formation of peroxynitrous acid ***(Goldstein et al., 1996)***.

NO reacts with target protein by direct nitrosylation. This has been termed "nitrosative stress" and has been implicated in the inactivation by NO of membrane ion channels such as N-methyl-D aspartate receptor, signaling proteins such as P21 ras, protein kinase, and the transcription factor oxy R ***(Lander et al., 1995)***.

NO binds to home group of soluble guanylate cyclase, activate this enzyme raising intracellular level of cGMP in many but not all types of cells ***(Clancy & Abramson, 1995)***. NO reacts with free thiols to form S- nitrosothiol compounds ***(Stamler et aL, 1992)***.

## NO biosynthesis and release:

NO biosynthesis is mentioned by ***Hecker et al., (1990)*** as follows: The initial step is a hydroxylation of nitrogen in guanidine group of L-arginine. The reaction is catalyzed by NO synthase (NOS), the process incorporates molecular oxygen into NO and citrulline. The reaction which is 5-electron oxidation requires reduced pyridine nucleotides, reduced biopteridines and calmodulin. Normally the levels of L-arginine are sufficient for continuous NO

biosynthesis. It is fascinating that the by-product citrulline is recycled back to L-arginine incorporating one nitrogen.

The modified urea cycle has two functions:

a) A secretory role to regenerate L-arginine for NOS.

b) Excretory role to eliminate excess nitrogen created by cellular mechanism.

***Moncada & Higgas (1993)*** mentioned that several isoforms of NOS has been identified, the most important are:

a) Constitutive NOS (CNOS) formed in endothelium and neuronal tissue.

b) Inducible NOS formed in activated immune cells and vascular smooth muscle cells.

| | Neuronal cNOS (NOS-1) | Endothelial cNOS (NOS-III) | Inducible NOS (NOS-II) |
|---|---|---|---|
| Present in | Central and Peripheral neurons, platelets, Pancreatic B cells Epithelial cell | Endothelial cells, Cardiac cells, neurons, myocytes | Macrophages, Ehdothelial cells, Chondrocytes, Smooth muscle cells, hepatocytes, Synoviocytes |
| Stimuli | NMDA, insulin, Thrombin | Acetyl choline, ADP, thrombin, shear stress | Endotoxin, Interferon-y, Mterleukin-1, TNF-a |
| Chromosomal Localization | 12(human) | 7 (human) | 17 (human), 11 (mouse) |
| Effect of calcium | Calcium dependant | Calcium dependant | Calcium Independant |
| Production of NO | Small quantities | Small quantities | Large quantities for very long periods |

Table (7): Contrasting properties of isoforms of nitric oxide synthase ***(Clancy et al., 1998)***

## Inhibition of nitric oxide synthase:

***Forchgott & Van Huotte (1989)*** mentioned that the synthesis of NO from L-arginine can be inhibited by analogous of L-arginine,

examples of these are N monomethyl L.arginine (LNMMA) and N-nitrol-arginine methylester (LNAME) that act by competing with L.arginine at the active site of NOS. Thus the action of LNMMA can be reversed by adding higher amounts of L.arginine. Also it was found that selenium containing antioxident inhibits both CNOS. In experimental studies NO may also be inhibited by the addition of oxyhaemoglobin and the effect of NO on guanylate cyclase can be blocked by methylene blue. On the other hand ***Roes et al., (1990)*** said that expression of inducible NOS can be prevented by prior administration of glucocorticoid.

## Mechanism of action of NO:

Most molecules that transmit signals between cells, such as hormones, neurotransmitters and growth factors, act through specific protein receptors that are often associated with the plasma membrane. In contrast, NO diffuses out of the cell that generates it and into target cells, where it interacts with specific molecular target ***(Lowenstein et al., 1994)***.

The best characterized receptor of NO is iron, contained in certain proteins as a haem group or as an iron-sulfur complex. NO exerts some of its effects by binding to iron-containing enzymes and either activating or inactivating the enzymes. When NO binds to the iron in the haem group of guanylate cyclase the enzyme is activated.

Guanylate cyclase then produces cGMP, and the increase in cGMP activates other cellular processes ***(Lowenstein et al., 1994).***

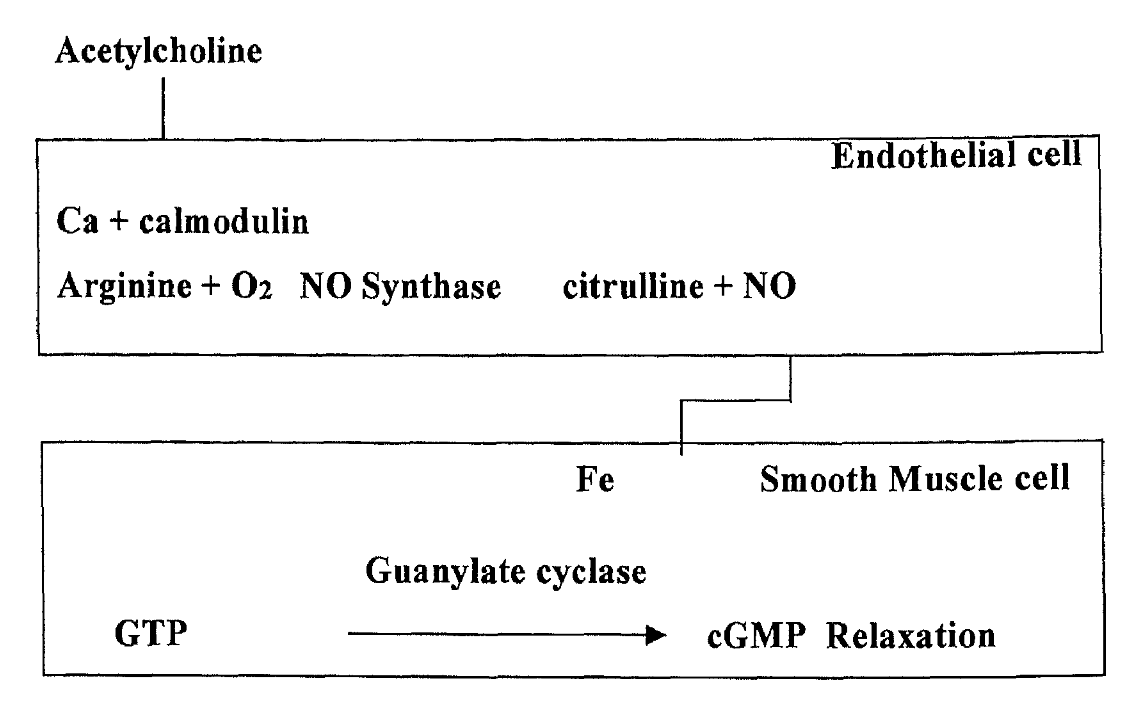



Fig (5): Action of Nitric oxide on arterial smooth muscle.

A messenger molecule such as acetylcholine binds to the acetylcoline receptor on endothelial cell. Activating inward calcium currents. Calcium binds to calmodulin and activates endothelial cell NOS, which converts arginine plus oxygen into cirtrulline and NO. NO diffuses out of the endothelial cell into an adjacent smooth muscle cell and activates guanylate cyclase by binding to the iron in its heme group. The increase in cGMP causes smooth muscle relaxation and thus vasodilatation. GTP: guanosine triphospate ***(Lowenstein et al, 1994).***

## Effects of NO on various systems:

I. Role of NO in the cardiovascular system.

II. Role of NO in Immunity.

III. Role of NO in the nervous system.

IV. Role of NO in respiratory system.

V. Role of NO as a free radical.

VI. Role of NO in gastroenterology.

VII. Role of NO in liver cirrhosis and portal hypertension.

## I. Role of NO in the Cardiovascular System

### 1- Role of NO in smooth muscle relaxation:

The vasculature is in a constant state of active dilatation mediated by NO. Endothelial cells continuously release small amounts of NO, producing a basal level of vascular smooth muscle relaxation.

When inhibitors of NOS, such as LNAMEor LNMMA, are infused into animals ***(Baylis et al., 1992 and Ikeda et al., 1992)*** or humans ***(Vallance et al., 1989)***, nitric oxide production is inhibited, vascular smooth muscle contracts and blood pressure increases. Because the half-life of NO in biological fluids is between 2 and 30 seconds, the effect of NO spontaneously diminishes and the vessel constricts unless more NO is produced. Shear-stress, an increase in blood flow through a vessel, is another physiological stimulus to

which endothelial cells respond by increasing NO production ***(Buga et al., 1991).***

Factors locally released by adjacent tissues, such as bradykinin, acetylcholine, can also induce NO release in some vessels but not in others. A basal level of NO regulates blood flow in the brain ***(Faraci & Breese, 1993)***, heart ***(Jones & Brody, 1992),*** lung ***(Fineman et al., 1991),*** gastrointestinal tract ***(Iwata et al., 1992),*** and kidney ***(Deng & Baylis, 1993).***

Thus NO is an endogenous autoregulater of blood flow. The release of NO into the vasculature is also controlled by the autonomic nervous system. Parasympathetic nerves containing NOS terminate in the adventitia of certain large vessels such as the cerebral and retinal arteries ***(Nozaki et al., 1993).***

NO is released from the nerves and diffuse into the muscular media from the outside of the vessel, causing vasorelaxation. However, NO is not the only vasodilator, and defects in other relaxation pathways could also cause endothelial dysfunction and contractile abnormalities however NO is anticipated to have a central role in the endothelial dysfunction and pathophysiology of atherosclerosis and essential hypertension, vasorelaxation is impaired in early atherosclerosis ***(Werns et al., 1989).***

And recent studies of coronary artery show that basal acid stimulated NO release are impaired in established disease, not Just at sites of atheroma but throughout the vessel, implying generalized endothelial dysfunction ***(Chester et al., 1990).*** Cholesterol, and especially its low-density lipoprotein fraction (LDL), may be responsible for such dysfunction, as both are known to impair endothelium dependent vasodilatation and NO release ***(Andrews et al., 1987).***

**3- Role of NO in hypertension and atherosclerosis:**

***Thimerman et al., (1993)*** mentioned that a decrease in NO generation has been postulated in endothelial dysfunction that may have a substantial effect on blood pressure and tissue blood flow. The role of NO synthesis in healthy vascular endothelium is to maintain arterial blood vessels in an active state of vasodilatation and continuous secretion to the luminal surface provides lubrication of the vascular wall to prevent platelets and leukocytes from sticking to it.

Vascular endothelial cells produce various biologically active factors regulating blood pressure, coagulation and possibly cell growth of the vascular wall. Of these factors, NO has been the subject of attention because of its quite simple molecular structure and a variety of biological functions ***(Naruse et al., 1999).***

It was found that in hypertensive patients endothelium dependent vasorelaxation and production of nitric oxide are impaired, possibly due to a deficiency of L. arginine and/or a disorder of its utilization. Also it was found that NO has antiatherogenic action, inhibits platelets function and proliferation of vascular smooth muscle cells, therefore, potentiation of endogenous NO synthesis or supplement of exogenous NO donors could be a novel therapeutic approach for treatment of hypertension and atherosclerosis, while potential adverse effects of NO including cytotoxicity, immunosuppressibility and hypotensive shock should be taken in consideration ***(Naruse et al., 1999).***

**3- Effects of NO on platelets function:**

NO inhibited platelet aggregation via a cGMP dependent mechanism ***(Mellion et al., 1981).***

Prostacyclin (which inhibit platelet aggregation via cAMP dependent mechanism) and NO acted synergistically to inhibit aggregation and to disaggregate platelets, suggesting that the release of NO and prostacyclin by the vascular endothelium plays a role in its thromboresistant properties. Furthermore, like prostacyclin, NO also has cytoprotective effects. Thus, the interaction of these two compounds might prove to have a superior antithrombotic effect to that of either of them alone ***(Sinzinger et al., 1990).***

NO also inhibits platelet adhesion to collagen fibrils and endothelial cell matrix ***(Radomski et al., 1987).***

## II. Role of NO in Immunity

***Yamamoto et al., (1998)*** said that NO is an important mediator of immune and inflammatory responses. Moreover NO has been suggested to play some role in the pathogenesis of autoimmune disorders, where it was investigated by ***Kime et al., (1988)*** who suggested that procytokines processing is required for maturation and release of interleukin 1 (IL-1) beta and IFN gamma-inducing factor from activated macrophages. They found that NO could suppress IL-1 beta and IGIF processing, providing evidence for a unique role for induced NO in regulating 1L-1 beta and IGIF release.

***Tanaka (1998)*** said that excessive nitric oxide synthesis by inducible NO synthase (INOS) has been implicated in the pathogenesis of inflammatory diseases such as rheumatoid arthritis by causing defect in lymphocytic function, thus selective inhibition of INOS might be beneficial for treatment of immunological abnormalities associated with inflammatory diseases.

### Role of NO in malignancy:

***Xiaot and Shun, (2000),*** suggested that NO and TNF- alpha produced by activated macrophages may be related to the

pathogenesis of malignant bone tumors. ***Moussa et al., (2000)*** found that NO is elevated in liver cirrhosis and haptocellular carcinoma.

**Role of NO in septic shock:**

There is definitive evidence that NO is the final common pathway leading to septic shock. Septic shock is initiated by endotoxins derived from bacterial cell walls that activate several humoral pathways and, most importantly, stimulate excessive cytokine release. Lipopolysaccarides (LPS), 1L-1,IFN and TNF are the principal mediators of inducible NO synthesis in endothelial cells and vasomotor cells, which are the propable cellular source of excessive intravascular NO release in septic shock ***(Calandra et al., 1990 and Ochoa et al., 1991).***

Moreover, it was found that in patients with sepsis, low doses of LNMMA restores the blood pressure and vascular responsiveness to pressure agents ***(Calver et al., 1993).***

**Role of NO in apoptosis:**

In this regard, NO has been also implicated in the apoptosis (programmed cell death). Different studies have revealed that stimulation and inhibition of different genes are required to stimulate apoptosis. Furthermore, the redox states of the cells play an important role through the effect of NO as a promoter of apoptosis ***(Lobez-Farre et al., 1998).***

NO promotes apoptosis in macrophages, thymocytes, chondrocytes, and pancreatic B islet cells ***(Fehsel et al., 1993).*** NO directly induces apoptosis in tumor cells ***(Cui et al., 1994).***

## III. Role of NO in the nervous system

Many studies have focused on the constitutive cNOS present in both the central and peripheral nervous systems although INOS has been described ***(Boje and Arora, 1992).*** Glutamate is an excitatory neurotransmitter acting on the N-methyl-D-aspartate receptor (NMDAr). NMDAr stimulation produces a post synaptic calcium influx resulting in NO synthesis by the calcium dependant cNOS. NO may act as a retrograde neurotransmitter acting on the guanylate cyclase (G-Case) of the presynaptic terminal to enhance neurotransmission. There is also strong evidence that NO mediates NMDA neurotoxicity. Clinical trials are currently evaluating NMDA receptor antagonists in acute stroke, but inhibition of NOS in a mouse model of acute stroke proved more effective in limiting brain damage than did NMDA receptor antagonists ***(Kolleger et al., 1993).***

Key sites of NO synthesis within the autonomic nervous system are non-adrenergic non-cholinergic (NANC) nerve terminals that generally serve to relax smooth muscle. NO mediated NANC function have been identified in the gastrointestinal tract. ***(Boeckxstaens et al., 1990)*** the respiratory system, arterial vessels,

also it has a role in penile erection and has a key role in gut sphincter control.

## IV. Role of NO in Respiratory system

NO may be a physiological mediator in the lung. It is present in lung epithelium and other pulmonary cells like activated macrophages and neutrophils and has been suggested to be a mediator of nerve dependent bronchodilatation. Reduced NO release may also be the mechanism underlying hypoxic pulmonary vasoconstriction (HPV). In HPV the blood through the lung is redirected to the best ventilated areas to maximize the oxygenation of the blood during its passage through the pulmonary circulation. The use of NOS inhibitors confirm that NO has an important role in the lung as these agents increase pulmonary vascular resistance, enhance HPV and cause hypoxia during spontaneous breathing. Inhalation of NO abolishes HPV in man. This was a strong evidence that NO is an important regulator in pulmonary circulation ***(Persson et al., 1994).***

Exhaled NO has been shown to be increased in patients with asthma and has been put forward as a mark of air way inflammation ***(Ho et al., 1998).***

In patients with liver cirrhosis, there is marked dilatation of the branches of the pulmonary arteries, this leads to perfusion/ventilation

mismatch with secondary hypoxaemia (hepatopulmonary syndrome). NO is incriminated for the occurrence of hepatopulmonary syndrome. Interleukin-1 was accused for activation of NOS enzyme in patients with liver cell failure. ***(Tarek et al., 2001).***

## V. Role of NO as a free radical

NO and superoxide ($O_2$) react to form a third free radical, peroxynitrite (ONOO) ***(Bechman et al., 1990)***. Two potential consequences of NO and O2 interaction and the resultant ONOO production may be provided: one results in increasing toxicity and the other reduces toxicity due to free radicals, under certain circumstances, the confined and limited production of toxic radicals is required, such as in the killing of target microorganisms or in the killing of tumor cells by activated immune cells. Increased production of oxygen free radicals is also a consequence of pathological states such as inflammation or transient ischaemia with reperfusion. Mere, NO may be produced in greater amounts to combine with $O_2$ for ONOO formation followed by non toxic degradation as the inactivation of toxic reactions by NO. NO could function to scavenge $O_2$, essentially remove $O_2$ through the rapid formation of ONOO. Inhibition of NO synthesis dramatically increases liver damage, which in turn can be inhibited by superoxide

dismutase in a model of endotoxin-induced liver injury **(Harbrecht, 1992)**.

## VI. Role of NO in gastroenterology

Under resting condition mucosal perfusion is regulated by NO derived from vascular endothelium of mesenteric bed. NO may protect gastrointestinal mucosa from a variety of stimuli by maintaining mucosal perfusion, inhibiting neutrophil adhesion to mesenteric endothelium, blocking platelets adhesion and preventing mast cell activation. However excessive NO may directly injure the mucosa ***(Saizam, 1995)***. In contrast, during inflammation, excessive NO production from inducible NOS may contribute to mucosal hyperemia. ***Boughton-Smith et al., (1993)*** mentioned that NOS activity in mucosa of ulcerative colitis patients was about ten folds more than control patients.

Also, coordination of peristalsis and sphincteric action is modulated by the release of NO that acts as peripheral neurotransmitter of NANC enteric nervous system. Alteration of bowel motility may result from excessive release of NO generated during endotoxemia and inflammatory bowel disease ***(Tomita et al., 1997)***.

***Mona et al., 2000*** reported that, increased gastric mucosal NOS activity in portal hypertensive gastropathy patients would

support an active hyperdynamic, rather than a passive congestion basis for the vascular mucosal changes in portal hypertensive gastropathy and also indicate that increased NOS activity may play an important role in the increased susceptibility of gastric mucosa to damage in those patients.

## VII. Role of NO in liver cirrhosis and portal hypertension

Hypotension, low systemic vascular resistance and reduced sensitivity to vasoconstrictors are features of hyperdynamic syndrome in portal hypertension (PH) and are pathogenic factors triggering most serious clinical complications of liver cirrhosis. NO is a powerful vasodilating agent, released from vascular endothelial cell and affecting relaxation of vascular smooth muscle. An increased release of NO has been proposed to play a role in the pathogenesis of vasodilatation and vascular hypocontractility associated with portal hypertension.

In agreement with this hypothesis, the whole body production of NO has been found to be increased in portal hypertension, and the measurement of NOS mRNA expression in different organs suggest that the splanchnic vascular system is a major source of NO release, consequently. NO could play a role in the development of the splanchnic hyperemia, collateral circulation and portal hypertensive gastropathy. By contrast PH-associated endothelial dysfunction

seems to invalidate the capability of intrahepatic and intrarenal vasculature to produce NO. A deficient release of NO in these vascular tributaries might contribute to enhancement of PH and development of the HRS ***(Hartleb et al., 1997).***

Cirrhosis is associated with several circulatory abnormalities. These include hyperkinetic systemic and splanchnic circulation, hepatopulmonary syndromes including pulmonary hypertension, and cirrhotic cardiomyopathy. Hepatopulmonary syndrome generally refers to hypoxaemia seen in patients with chronic liver disease and appears to be relatively common, although often subclinical. However, significant pulmonary hypertension occurs in 0.2-0.7% of cirrhotic patients. NO and/or other vasodilators appear to be involved in the pathogenesis of hepatopulmonary syndrome through induction of pulmonary capillary dilatation which increases the alveolar-arterial oxygen gradient ***(Lee, 1998).***

There is evidence that support a role of NO in the hyperdynamic circulation of cirrhosis and suggests that bacterial lipopolysacchride endotoxin may be triggering for increase endothelial NO formation. They are:

1- Endogenous NO is an important modulator of vascular tone in animals and humans.

2- Agonist-induce release of endogenous NO leads to haemodynamic response similar to hyperdynamic circulation of cirrhosis.
3- Endotoxin is found in high circulatory levels in cirrhosis and may trigger endothelial NO synthesis leading to hyperdynamic circulation in animals and human.
4- Urinary cGMP levels are increased in cirrhotic humans possibly due to increase NO production leading to increased cGMP.
5- Endogenous NO production mediates systemic and splanchnic vasodilatation in portal hypertensive rats.
6- Methyllene blue, a blocker of NO action elevated blood pressure in patients with cirrhosis and severe hypotension.
7- NO producing drugs might be effective treatment of portal hypertension.
8- Molsidomine (NO donor) acutely reduces portal pressure in cirrhotic rates and humans. ***(Epstein and Goligorsky, 1997).***

## Role of Nitric oxide (NO) in spontaneous bacterial peritonitis (SBP)

Cirrhosis is characterized by an increased risk for the development of infections, in particular SBP, an infection of ascites that occurs in patients with severe liver disease. ***(Garcia-Tsao et al, 1998).***

***Bories et al., (1997)*** said that SBP in cirrhotic patients led to a long lasting increased total production of NO. This overproduction (which become maximum approximately two weeks after infection) may contribute to maintaining splanchnic vasodilatation and thus worsen the hyperkinetic state in these patients.

Peritoneal cells from cirrhotic patients were able to express high levels of NO. However, other sources may be considered as possible contributors to NO hyperproduction, since iNOS messenger RNA and protein have been detected in duodenum, ileum, colon, and mesenteric vessels from rats with sepsis after endotoxin injection ***(Martini et al., 1996 and Chen et al., 1996).***

Furthermore, NO production may have a detrimental effect on mucosal barrier function, thus favoring bacterial translocation and recurrence of SBP in cirrhotic patients ***(Jiménez et al., 1999)***.

It was found that patients with high NOx levels had a significantly greater Child score with more encephalopathy and a poor nutrition than patients with low ascites NOx levels. Also, mortality rate was found to be significantly higher in patients with SBP who had elevated ascites NOx ***(Garcia-Tsao et al, 1998).***

## Nitric oxide and Hepatorenal syndrome

It acts as potential important mediator of renal failure in general, thus suggesting that they might also contribute to renal dysfunction in the setting of advanced hepatic disease ***(Baylis et al., 1992).***

Endogenous NO is synthesized by NOS which use L-arginine as substrate. The various isoforms of NOS are widely distributed within the kidney. NO synthesized by inducible (iNOS), and possibly bNOS (brain NOS), has a major role in control of renal vascular tone, via its vasodilatory actions. Generalized systemic NO inhibition (NOI) leads to dose dependent increases in blood pressure (BP) and renal vascular resistance (RVR), a large fall in renal plasma flow (RPF) and a slight fall in glomerular filtration rate (GFR) ***(Raij & Baylis, 1995).***

In addition to directly influencing vascular tone via iNOS, NO at the Juxta glomerular apparatus (JGA). JGA controls glomerular haemodynamics via the tubuloglomerular feedback mechanism. Also, NO plays complex roles in control of JGA renin release ***(Ito, 1995)*** and the physiological relationship between NO and renin has not yet been defined.

NO also influences sodium excretion and may play a physiological role in control of sodium balance. NO has a direct

tubular effect to inhibit sodium reabsorption in the collecting duct. It is likely that NO controls sodium excretion both by direct tubular actions and also by regulating the vascular tone in the medullary circulation ***(Baylis et al., 1992).***

**Over production of NO:**

There is increasing evidence that elevated levels of NO play a primary pathogenic role in some forms of immune-mediated glomerular injury excessive NO is cytotoxic by several mechanisms, including formation of peroxynitrite and nitrosylation and inactivation of various enzymes. Some end-stage renal failure patients develop severe hypotension during haemodialysis due to iNOS activation in vascular smooth muscle, secondary to bio-incompatibility of the dialysis membranes ***(Raij et al., 1995)***

**NO deficiency status:**

The clinical importance of NO deficiency in essential hypertension is not yet clear although functional studies suggest that NO-mediated vasodilatation is attenuated in some vascular beds of some individuals with essential hypertension ***(Baylis et al., 1992).*** There is evidence suggesting that NO deficiency occurs in end stage renal patients, since the 24-h production of stable NO oxidation products $NO_2$ + $NO_3$ are reduced in peritoneal dialysis patients ***(Schmidt et al., 1996).*** In renal failure NO deficiency presumably

results both from reduced arginine availability (since the kidney is a major site of endogenous arginine synthesis), and accumulation of endogenous NOIs secondary to decreased renal clearance ***(Reyes et al., 1994).*** L-arginine supplementation provides a promising therapeutic role for patients with various forms of progressive renal disease ***(Reyes et al., 1994).***

Acute L-arginine infusion in patients with chronic glomerulo-nephritis has already been shown to substantially reduces the proteinuria ***(Wolf et al., 1995).*** In conclusion NO plays a key role in the physiological regulation of renal blood flow and glomerular haemodynamics and possibly also in control of sodium excretion. In some disease states NO over-or underproduction may play a primary role in the disease process and chronic L-arginine supplementation may provide a useful tool in the treatment of various forms of renal disease.

**NO in decompansated liver cirrhosis and hepatorenal syndrome:**

Several investigators have demonstrated NO over production as assessed by elevated level of $NO_2$ and $NO_3$ in patients with advanced liver disease ***(Epstein & Goligorsky, 1997).*** It is also shown that NOS activity increases as the Child-Pugh's score increase, and hence hepatic dysfunction increases and that this is associated with progressive decrease in systolic and diastolic blood pressure. These

data provide further evidence for the possible involvement of NO in the pathophysiology of the vasodilatation and hyperdynamic circulation of liver disease. These heamodynamic disturbances will contribute to worsening hepatic and renal dysfunction ***(Helen et al., 1998).***

In summary, patients with decompensated cirrhosis have elevated levels of nitrate. Elevated NO levels in these patients are due to increased production and not impaired metabolism, and treatment with nitrates may enhances the hyperdynamic state in patients with decompensated cirrhosis ***(Barak et al., 1999).*** An increase in the intrahepatic resistance to portal venous flow in cirrhosis is an important factor in the development and maintenance of portal hypertension ***(Grozmann & Jensen, 1996).*** Enhanced contractility of the hepatic perisinusoidal stellate cells, also called lipocyte or Ito cells, has been implicated as one cause of increased hepatic sinusoidal resistance in the cirrhotic liver ***(Rockey, 1997).*** Lipocyte contractility is regulated by a counterbalance of the effects of agents such as endothelin which promote contraction of the lipocytes and smooth muscle relaxing agents such as NO ***(Kawada et al., 1993 and Rockey & Chung, 1995).***

A decrease in NO activity may therefore promote portal hypertension through an increase of the hepatic sinusoidal resistance.

In addition there is abnormal dilatation of the mesenteric vascular bed, and decreased responsiveness to vasoconstrictor agents and increased activity of on endogenous vasodilator agents, the principle one is NO. ***Sarela et al., (1999)*** have studied the NO activity in the liver and splanchnic vascular bed of patients with cirrhosis and they found that, the activity of cNO release in intrahepatic vascular tributaries NO is diminished in cirrhotic human liver. The resultant decrease may promote an increase in the intrahepatic portal vascular pressure. Elevated portal venous ($NO_2$+$NO_3$) indicates enhanced splanchnic vascular release of NO in cirrhotic patients, but the absence of increased NOS activity in the mesenteric vasculature suggests differential regulation of NO synthesis within the splanchnic vascular bed.

In addition to deficient release of NO by intrahepatic vasculature, there is also deficient release of NO by intrarenal vasculature this leads to the development of HRS ***(Hartleb et al., 1997)*** and it has been suggested that serum nitrite/nitrate levels are highest in patients with functional renal failure (i.e. HRS) and these levels correlate with the magnitude of endotoxemia and there is a reset balance between vasoconstrictor and vasodilatory stimuli may contribute to the renal heamodynamic abnormalities that characterize the renal functional abnormalities of liver disease ***(Epstein & Goligorsky, 1997)***.

# PATIENTS & METHODS

# PATIENTS AND METHODS

This study was conducted on four groups of patients with liver cirrhosis chosen from in-patient admitted to internal medicine department in Ain Shams University Hospital:

- **Group (A)** included 10 patients with SBP and renal impairment.
- **Group (B)** included 10 patients with SBP with normal renal function.
- **Group (C)** included 10 patients with sterile ascitic fluid with renal impairment.
- **Group (D)** included 10 patients with sterile ascitic fluid with normal renal function.

The four groups were age and sex matched.

## Criteria of inclusion:

The patients with SBP were selected according to ***Runyon and Hoefs, (1984b)*** who defined SBP by:

1) An ascitic fluid neutrophil count greater than or equal to 250 cell/ml.
2) A positive ascitic fluid culture.
3) The lack of an obvious intra-abdominal source of infection.

The patients with HRS were selected according to International Ascites Club's Diagnostic Criteria of Hepatorenal syndrome ***(Arroyo et al., 1996).***

## Criteria of exclusion:

Patients with recent gastrointestinal bleeding, cardiac troubles, diabetes mellitus, malignant ascites and chronic renal failure were excluded from this study.

All patients were subjected to:

1- Full medical history taking and clinical examination.

2- Liver profile:
   - Serum albumin, ALT, AST, Total bilirubin, Direct bilirubin, Prothrombin time and Total plasma proteins.

3- Kidney function tests:
   - Serum creatinine, Blood urea nitrogen (BUN) and creatinine clearance.

4- Serum electrolytes:
   - Serum sodium and serum potassium.

5- Urinary sodium in 24 hours.

6- Ascitic fluid sample obtained under complete aseptic condition by abdominal paracentesis for :
   - Bacteriological analysis (culture & sensitivity),
   - Chemical analysis for:

a- Ascitic fluid total protein.

b- Ascitic fluid lactate dehydrogenase.

c- Ascitic fluid glucose.

7- Pelviabdominal U/S.

8- Routine Urine analysis.

9- Estimation of serum and ascitic nitric oxide level:

The transient and volatile nature of NO makes it unsuitable for most convenient detection methods. However, since most of the NO is oxidized to nitrite ($NO_2$) and nitrate ($NO_3$), the concentrations of these anions have been used as a quantitative measure of NO production ***(Granger et al., 1990).***

R&D Systems Total Nitric Oxide Assay involves the conversion of nitrate to nitrite by the enzyme nitrate reductase. The detection of total nitrite is then determined as a colored azo dye product of the Griess Reaction that absorbs visible light at 540 nm.

**Principle of the assay:**

This assay determines total nitric oxide based on the enzymatic conversion of nitrate to nitrite by nitrate reductase. The reaction is followed by a calorimetric detection of nitrite as an azo dye product of the Griess Reaction. The Griess Reaction is based on the two-step diazotization reaction in which acidified $NO_2$ produces a nitrosating

agent, which reacts with sulfanilamide acid to produce the diazonium ion. This ion is then coupled to *N*- (1-naphthyl) ethylenediamine to form the chromophoric azo-derivative which absorbs light at 540 nm.

**Sample collection and storage:**

**Serum:**

Five ml blood was collected after an over night fast from the anticubital vein using a sterile plastic syringe. Blood was transferred into clean dry tubes & left to clot. Prompt separation of serum was carried out without delay after centrifugation for 10 minutes at approximately 1000 xg. The serum was put in aliquots & stored at -20°C until the time of assay.

**Ascitic fluid:**

Five ml ascitic fluid was collected using a sterile plastic syringe. Ascitic fluid was transferred into clean dry tubes, and there were separated by centrifuge. The supernatant was assayed to detect excreted NO in the media.

**Reagents:**

- Nitrate reductase (Aspergillus species).
- NADPH.
- FAD.
- Sulfanilamide (1 gm / 100ml 2.5% phosphoric acid).
- N- (1-Naphthyl) ethylenediamine dihydrochloride (0.5 g/100

ml 2.5% phosphoric acid).

- 2.5% phosphoric acid.

**Assay procedure:**

1- Nitrate was estimated as nitrite after enzymatic conversion by nitrate reductase, NADPH, FAD and nitrate reductase (from aspergillus species) were added to a 450 μl serum sample to yield a final concentration of 50 μmol/L 5 μmol/L and 0.1 unit/ml respectively, samples were subsequently incubated for 20 minutes at 37 C°.

2- Total nitrite and nitrate (nitrite + reduced nitrate) were assayed with Greiss reagent. The Latter is composed of 1 g/100 ml sulfanilamide in 2.5% phosphoric acid and 0.5 g/100 ml N-l-naphthylethyl-enediamine in 2.5% phosphoric acid. 0.8 of each were added to 0.4 ml of the incubated mixture.

3- The mixture was incubated at room temperature for 10 minutes. The absorbance was read against blank at 540 nm.

# Statistical methods

The data collected was processed to a personal computer IBM. The data was analyzed by using the program ***(SPSS)*** for windows version (8). "Statistical package for social science".

## - Descriptive statistics:

1) **Quantitative data:** were described by:

   - Mean.
   - Standard deviation (± SD).
   - Range (minimum-maximum).

2) **Qualitative data:** were described by frequency and percentage (%).

## - Analytical statistics:

**1) For comparing different groups:**

**a) Quantitative data:**

- Student t-test (t) of two independent to compare between each two groups.

**b) Qualitative data:**

- Chi-square test.

**2) To find a relation between different variables by:**

Pearson's test: Correlation coefficient test (r-test).

## - Level of significance = P value:

$P > 0.05$ = insignificant.

$P < 0.05$ = significant.

$P < 0.01$ = highly significant.

# RESULTS

# RESULTS

The current study was carried out on 40 patients with chronic liver disease and ascites. According to the results of the ascitic fluid analysis and kidney function tests, they were divided into four groups:

**Group (A):**

Included 10 patients with SBP and HRS. This group included 7 males (70%) and 3 females (30%), there ages ranged from 46 - 56 years, with a mean of (50.5 ± 3.4) years.

**Group (B):**

Included 10 patients with SBP without HRS. This group included 8 males (80%) and 2 females (20%), there ages ranged from 42 - 56 years, with a mean of (49.2 ± 4.9) years.

**Group (C):**

Included 10 patients with HRS without SBP. This group included 7 males (70%) and 3 females (30%), there ages ranged from 40 - 56 years, with a mean of (50.9 ± 5.3) years.

**Group (D):**

Included 10 patients with sterile ascites without HRS. This group included 8 males (80%) and 2 females (20%), there ages ranged from 48 - 60 years, with a mean of (52.5 ± 3.8) years.

The four groups were matched as regard age and sex distribution with no significant difference (P > 0.05).

∢ **Table (8)** shows comparison between group A, B, C, D as regard age distribution, with the following results:

Mean ages ± SD for group A, B, C, D were 50.5 ± 3.4, 49.2 ± 4.9, 50.9 ± 5.3, 52.5 ± 3.8 respectively.

There was no statistically significant difference between these groups with P > 0.05.

∢ **Table (9)** shows comparison between group A, B, C, and D as regard sex with the following results:

There was no statistically significant difference between these groups with P > 0.05.

∢ **Table (10)** shows comparison between group A, B, C, and D as regard clinical data with the following results:

**As regard fever:** it was present in 2 (20%) patients in group (A), 2 (20%) patients in group (B) while there was no patients with fever in group (C) or (D).

**As regard jaundice:** it was present in 6 (60%) patients in group (A), 6 (60%) patients in group (B), 3 (30%) patients in group (C) and in 3 (30%) patient in group (D).

**As regard abdominal pain:** it was present in 6 (60%) patients in group (A), 4 (40%) patients in group (B) and 2 (20%) patients in group (C) while there was no patients with abdominal pain in group (D).

**As regard encephalopathy:** it was present in 6 (60%) patients in group (A), 4 (40%) patients in group (B) and 3(30%) patients in group (C) while there was no patients with encephalopathy in group (D).

There was a statistically significant difference between these groups as regard abdominal pain ($P < 0.05$) and highly significant difference as regard encephalopathy ($P < 0.01$). Other parameters showed statistically insignificant difference between these groups ($P > 0.05$).

- **Table (11,12,13,14,15,16)** shows comparison between group A, B, C, and D as regard liver profile, kidney function, blood picture, ascitic fluid analysis, serum and ascitic NO.

**As regard the mean value of ALT,** there was a statistically insignificant difference between the four groups ($P > 0.05$).

**As regard the mean value of AST,** there was a statistically insignificant difference between the four groups ($P > 0.05$).

**As regard the mean value of total bilirubin,** there was a statistically significant difference between group A and group D ($P < 0.05$), the mean total bilirubin was higher in group A (4.46 ± 3) than group D (2.21 ± 1.1). Also there was a statistically significant difference between group B and group D ($P < 0.05$), the mean total bilirubin was higher in group B (8.25 ± 8.6) than group D (2.21 ± 1.1). While there was insignificant difference between group C and group D ($P > 0.05$).

**As regard the mean value of direct bilirubin,** there was a statistically significant difference between group A and group D ($P < 0.05$), the mean direct bilirubin was higher in group A (2.37 ± 1.9) than group D (0.77 ± 0.45). Also there was a statistically significant difference between group B and group D ($P < 0.05$), the mean direct bilirubin was higher in group B (4.49 ± 5) than group D (0.77 ± 0.45). While there was insignificant difference between group C and group D ($P > 0.05$).

**As regard the mean value of serum albumin,** there was a statistically significant difference between group A and group B ($P < 0.05$), the mean serum albumin was lower in group A (1.87 ± 0.5) than group B (2.2 ± 0.5). While there was a statistically highly significant difference between group A and D ($P < 0.01$), the mean

serum albumin was lower in group A (1.87 ± 0.5) than group D (2.63 ± 0.4).

Also there was a statistically significant difference between group B and group D ($P < 0.05$), The mean serum albumin was lower in group B (2.2 ± 0.5) than group D (2.63 ± 0.4). Also there was a statistically significant difference between group C and group D ($P < 0.05$), The mean serum albumin was lower in group C (2.01 ± 0.3) than group D (2.63 ± 0.4).

**As regard the mean value of prothrombin time**, there was a statistically significant difference between group A and group D ($P < 0.05$), the mean prothrombin time was higher in group A (19.95±6) than group D (16.14± 1.2). There was a statistically significant difference between group B and group D ($P < 0.05$). The mean prothrombin time was higher in group B (17.53± 4) than group D (16.14± 1.2). Also there was a statistically significant difference between group C and group D ($P < 0.05$). The mean prothrombin time was higher in group C (17.73± 2.1) than group D (16.14± 1.2).

**As regard the mean value of serum creatinine**, there was a statistically highly significant difference between group A and both groups B and D ($P < 0.01$), the mean serum creatinine was higher in group A (2.35 ± 1) than Group B (0.89 ± 0.3) and group D (0.93 ± 0.13). Also between group C and both groups B and D. ($P < 0.01$),

the mean serum creatinine was higher in group C (2.39 ± 0.8) than group B (0.89 ± 0.3) and group D (0.93 ± 0.13).

**As regard the mean value of BUN,** there was a statistically highly significant difference between group A and both groups B and D. ($P < 0.01$), the mean BUN was higher in group A (40.9 ± 13.5) than Group B (15.4 ± 5.7) and group D (13.3 ± 3.9). Also between group C and both groups B and D. ($P < 0.01$), the mean BUN was higher in group C (42.9 ± 14.3) than group B (15.4 ± 5.7) and group D (13.3 ± 3.9).

**As regard the mean value of creatinine clearance,** there was a statistically highly significant difference between group A and both groups B and D. ($P < 0.01$), the mean creatinine clearance was lower in group A (46.03 ± 14.9) than Group B (96.31 ± 18.4) and group D (103.69 ± 11.2). Also between group C and both groups B and D. ($P < 0.01$), the mean creatinine clearance was lower in group C (50.08 ± 14.2) than group B (96.31 ± 18.4) and group D (103.69 ± 11.2).

**As regard the mean value of urinary sodium,** there was a statistically highly significant difference between group A and both groups B and D. ($P < 0.01$), the mean urinary sodium was lower in group A (27.9 ± 2.8) than Group B (64.5 ± 7.2) and group D (62.5 ± 5.5). Also between group C and both groups B and D. ($P < 0.01$), the

mean urinary sodium was lower in group C (27.5 ± 2.3) than group B (64.5 ± 7.2) and group D (62.5 ± 5.5).

**As regard the mean value of serum sodium,** there was a statistically highly significant difference between group A and both groups B and D. ($P < 0.01$), the mean serum sodium was lower in group A (127.6 ± 1.5) than Group B (134.8 ± 3.9) and group D (134.7 ± 4.9). Also between group C and other groups A, B and D. ($P < 0.01$), the mean serum sodium was lower in group C (120.3 ± 5.9) than group A (127.6 ± 1.5), group B (134.8 ± 3.9) and group D (134.7 ± 4.9).

**As regard the mean value of serum potassium,** there was a statistically significant difference between both groups A and B with group D. ($P < 0.01$), the mean serum potassium was higher in both groups A(4.53 ± 0.5) and group B (4.63 ± 0.6) than group D (4 ± 0.4).

**As regard the mean value of white blood cell count,** there was a statistically significant difference between group A and group C ($P < 0.05$), the mean white blood cell count was higher in group A (10.99 ± 4.6) than group C (7.83 ± 2.5), while there was a statistically highly significant difference between group A and group D ($P < 0.01$), the mean white blood cell count was higher in group A (10.99 ± 4.6) than group D (5.31 ± 1.1).

Also B & C, while there was a statistically highly significant difference between group B and group D ($P < 0.01$), the mean white blood cell count was higher in group B (10.11 ± 5.5) than group D (5.31 ± 1.1).

**As regard the mean value of hemoglobin**, there was a statistically significant difference between group A and group D ($P < 0.05$), the mean hemoglobin was lower in group A (9.3 ± 1.2) than group D (10.39 ± 0.9).

**As regard the mean value of platelet count,** there was a statistically highly significant difference between group A and group D ($P < 0.01$), the mean platelet count was lower in group A (77.9 ± 25.1) than group D (119.5 ± 71.6).

Also there was a statistically significant difference between group B and group D ($P < 0.05$), the mean platelet count was lower in group B (92.4 ± 20.7) than group D (119.5 ± 71.6).

While there was a statistically insignificant difference between group C and group D ($P > 0.05$).

**As regard the mean value of cell count in the ascitic**, there was statistically highly significant difference between group A and both group C and group D ($P < 0.01$), the mean cell count in the ascitic was higher in group A (1210 ± 931) than in both group C (130 ± 52.2 ) and group D (68.2 ± 30.0).

Also there was statistically highly significant difference between group B and both group C and group D ($P < 0.01$), the mean cell count in the ascitic fluid was higher in group B (628± 519.5) than in both group C (130 ± 52.2) and group D (68.2 ± 30.0).

**As regard the mean value of ascitic total proteins**, there was a statistically significant difference between group A and group D ($P < 0.05$), the mean ascitic total proteins was lower in group A (1.66 ± 0.6) than group D (1.99 ± 1.9).

Also there was a statistically significant difference between group B and both groups C and group D ($P < 0.05$), the mean ascitic total proteins was lower in group B (1.35 ± 0.8) than group C (1.82 ± 0.99) and than group D (1.99 ±1.9).

While there was a statistically insignificant difference between group C and group D ($P > 0.05$).

**As regard the mean value of ascitic lactic dehydrogenase,** there was a statistically significant difference between group A and group B ($P < 0.05$), the mean ascitic lactic dehydrogenase was higher in group A (487.8 ± 293.3) than group B (256± 140.9) while there was a statistically highly significant difference between group A and both group C and group D ($P < 0.01$), the mean ascitic lactic dehydrogenase was higher in group A (487.8 ± 293.3) than group C (175.5 ± 62.5) and group D (167.3± 66.3).

Also there was a statistically significant difference between group B and both group C and group D ($P < 0.05$), the mean ascitic lactic dehydrogenase was higher in group B (256 ± 140.9) than both group C (175.5 ± 62.5) and group D (167.3 ± 66.3).

While there was a statistically insignificant difference between group C and group D ($P > 0.05$).

**As regard the mean value of glucose in the ascitic fluid,** there was a statistically insignificant difference between group A and group B ($P > 0.05$).

While there was a statistically significant difference between group A and both group C and D ($P < 0.05$), the mean glucose in the ascitic fluid was lower in group A (105 ± 22.1) than group C (181.3 ± 56.6) and group D (139.3 ± 43).

Also there was a statistically significant difference between group B and both group C and group D ($P < 0.05$), the mean the mean glucose in the ascitic fluid was lower in group B (92.3 ± 39.9) than group C (181.3 ± 56.6) and group D (139.3 ± 43).

While there was a statistically insignificant difference between group C and group D ($P > 0.05$).

**As regard the mean value of serum nitric oxide end products,** there was a statistically significant difference between group A and both group B and group C, ($P < 0.05$) the mean serum

nitric oxide end products was higher in group A (226.2 ± 96.8) than group B (134.7 ± 85.6) and group C (208.5 ± 135.8).

While there was a statistically highly significant difference between group A and group D ($P < 0.01$), the mean serum nitric oxide end products was higher in group A (226.2 ± 96.8) than group D (114.4 ± 43.7).

There was a statistically insignificant difference between and group B and group C, ($P > 0.05$), but the mean serum nitric oxide end products was higher in group C (208.5 ± 135.8) than group B (134.7 ± 85.6).

There was statistically significant difference between group B and group D, ($P < 0.05$) the mean serum nitric oxide end products was higher in group B (134.7 ± 85.6) than group D (114.4 ± 43.7).

There was statistically significant difference between group C and group D, ($P < 0.05$) the mean serum nitric oxide end products was higher in group C (208.5 ± 135.8) than group D (114.4 ± 43.7).

**As regard the mean value of ascitic nitric oxide end products,** there was a statistically significant difference between group A and both of group B and group C, ($P < 0.05$) the mean ascitic nitric oxide end products was higher in group A (320.1 ± 190.4) than group B (191.2 ± 113.3) and group C (135.7 ± 76.9).

While there was a statistically highly significant difference between group A and group D ($P < 0.01$), the mean ascitic nitric

oxide end products was higher in group A (320.1 ± 190.4) than group D (99.7 ± 8.9).

There was a statistically insignificant difference between and group B and group C, ($P > 0.05$), but the mean ascitic nitric oxide end products was higher group B (191.2 ± 113.3) than in group C (135.7 ± 76.9).

While there was a statistically insignificant difference between group C and group D ($P > 0.05$).

- **Table (17)** shows correlation between level of both serum and ascitic nitric oxide end products and different parameters in the studied groups ( in the patients as whole) with the following results:

There was a statistically insignificant correlation between both serum and ascitic nitric oxide end products and age, ($P > 0.05$).

There was a statistically insignificant correlation between both serum and ascitic nitric oxide end products and both ALT and AST, ($P > 0.05$).

There was a statistically significant positive correlation between both serum and ascitic nitric oxide end products and both total and direct bilirubin, ($P < 0.05$).

There was a statistically highly significant positive correlation between both serum and ascitic nitric oxide end products and prothrombin time, ($P < 0.01$).

There was a statistically highly significant negative correlation between both serum and ascitic nitric oxide end products and serum albumin, ($P < 0.01$).

There was a statistically significant positive correlation between both serum and ascitic nitric oxide end products and serum creatinine, ($P < 0.05$).

There was a statistically significant positive correlation between both serum and ascitic nitric oxide end products and BUN, ($P < 0.05$).

There was a statistically significant positive correlation between both serum and ascitic nitric oxide end products and creatinine clearance, ($P < 0.05$).

There was a statistically significant negative correlation between both serum and ascitic nitric oxide end products and urinary sodium, ($P < 0.05$).

There was a statistically insignificant correlation between both serum and ascitic nitric oxide end products and serum sodium and serum potassium, ($P > 0.05$).

There was a statistically significant positive correlation between serum nitric oxide end products and white blood cell count, ($P < 0.05$), while there was statistically highly significant positive correlation between ascitic nitric oxide end products and white blood cell count, ($P < 0.01$).

There was a statistically insignificant correlation between both serum and ascitic nitric oxide end products and both hemoglobin and platelet count, ($P > 0.05$).

There was a statistically highly significant positive correlation between both serum and ascitic nitric oxide end products and ascitic fluid cell count, ($P < 0.01$).

There was a statistically insignificant correlation between both serum and ascitic nitric oxide end products and total protein, ($P > 0.05$).

There was a statistically highly significant positive correlation between both serum and ascitic nitric oxide end products and ascitic lactic dehydrogenase enzyme, ($P < 0.01$).

There was a statistically insignificant correlation between both serum and ascitic nitric oxide end products and ascitic fluid glucose, ($P > 0.05$).

**Table (8):** Age distribution among the studied groups.

| Variable | Group A (n=10) | | Group B (n=10) | | Group C (n=10) | | Group D (n=10) | | P-value | Sign. |
|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | **SD** | **Mean** | **SD** | **Mean** | **SD** | **Mean** | **SD** | | |
| **Age** | 50.5 | 3.4 | 49.2 | 4.9 | 50.9 | 5.3 | 52.5 | 3.8 | > 0.05 | Insign. |

**Table (9):** Gender distribution among the studied groups.

| Variable | | Group A (n=10) | | Group B (n=10) | | Group C (n=10) | | Group D (n=10) | | P-value | Sign. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **No.** | **%** | **No.** | **%** | **No.** | **%** | **No.** | **%** | | |
| **Sex** | **Male** | 7 | 70 | 8 | 80 | 7 | 70 | 8 | 80 | > 0.05 | Insign. |
| | **Female** | 3 | 30 | 2 | 20 | 3 | 30 | 2 | 20 | | |

**Table (10):** Comparison between group A, B, C, D as regard clinical data.

| Variable | | Group A (n = 10) | | Group B (n = 10) | | Group C (n = 10) | | Group D (n = 10) | | P-value | Sign. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | No. | % | No. | % | No. | % | No. | % | | |
| Fever | +ve | 2 | 20 | 2 | 20 | 0 | 0 | 0 | 0 | > 0.05 | Insign. |
| | -ve | 8 | 80 | 8 | 80 | 10 | 100 | 10 | 100 | | |
| Jaundice | +ve | 6 | 60 | 6 | 60 | 3 | 30 | 3 | 30 | > 0.05 | Insign. |
| | -ve | 4 | 40 | 4 | 40 | 7 | 70 | 7 | 70 | | |
| Abdominal pain | +ve | 6 | 60 | 4 | 40 | 2 | 20 | 0 | 0 | < 0.05 | Sign. |
| | -ve | 4 | 40 | 6 | 60 | 8 | 80 | 10 | 100 | | |
| Encephalo-pathy | +ve | 6 | 60 | 4 | 40 | 3 | 30 | 0 | 0 | < 0.01 | Highly sign. |
| | -ve | 4 | 40 | 6 | 60 | 7 | 70 | 10 | 100 | | |

**Table (11):** Comparison between group A and group B as regards different variables.

| Variable | | Group A (n = 10) | | Group B (n = 10) | | P-value | Sign. |
|---|---|---|---|---|---|---|---|
| | | Mean | ± SD | Mean | ± SD | | |
| Liver Profile | ALT | 51.4 | 38.9 | 90.2 | 103.6 | > 0.05 | Insign. |
| | AST | 79.5 | 29.7 | 135.6 | 92.2 | > 0.05 | Insign. |
| | T. BIL | 4.46 | 3 | 8.25 | 8.6 | > 0.05 | Insign. |
| | D. BIL | 2.37 | 1.9 | 4.49 | 5 | > 0.05 | Insign. |
| | S. Alb. | 1.87 | 0.5 | 2.2 | 0.5 | < 0.05 | Sign. |
| | PT | 19.95 | 6 | 17.53 | 4 | > 0.05 | Insign. |
| Renal Func. Test | S. Cr. | 2.35 | 1 | 0.89 | 0.3 | < 0.01 | Highly sign. |
| | BUN | 40.9 | 13.5 | 15.4 | 5.7 | < 0.01 | Highly sign. |
| | Cr. Clearance | 46.03 | 14.9 | 96.31 | 18.4 | < 0.01 | Highly sign. |
| Urinary Na | | 27.9 | 2.8 | 64.5 | 7.2 | < 0.01 | Highly sign. |
| S.Na | | 127.6 | 1.5 | 134.8 | 3.9 | < 0.01 | Highly sign. |
| S.K | | 4.53 | 0.5 | 4.63 | 0.6 | > 0.05 | Insign. |
| Blood picture | WBCs | 10.99 | 4.6 | 10.11 | 5.5 | > 0.05 | Insign. |
| | Hb | 9.3 | 1.2 | 10 | 1.6 | > 0.05 | Insign. |
| | Platelet | 77.9 | 25.1 | 92.4 | 20.7 | > 0.05 | Insign. |
| Ascitic fluid | Cell count | 1210 | 931 | 628 | 519.5 | > 0.05 | Insign. |
| | T. protein | 1.66 | 0.6 | 1.35 | 0.8 | > 0.05 | Insign. |
| | LDH | 487.8 | 293.3 | 256 | 140.9 | < 0.05 | Sign. |
| | Glucose | 105 | 22.1 | 92.3 | 39.9 | > 0.05 | Insign. |
| NO | Serum | 226.2 | 96.8 | 134.7 | 85.6 | < 0.05 | Sign. |
| | Ascites | 320.1 | 190.4 | 191.2 | 113.3 | < 0.05 | Sign. |

**Table (12):** Comparison between group A and group C as regards different variables.

| Variable | | Group A (n = 10) | | Group C (n = 10) | | P-value | Sign. |
|---|---|---|---|---|---|---|---|
| | | Mean | ± SD | Mean | ± SD | | |
| Liver Profile | ALT | 51.4 | 38.9 | 28.8 | 7.1 | > 0.05 | Insign. |
| | AST | 79.5 | 29.7 | 63.8 | 27.7 | > 0.05 | Insign. |
| | T. BIL | 4.46 | 3 | 3.42 | 4 | > 0.05 | Insign. |
| | D. BIL | 2.37 | 1.9 | 1.55 | 2.4 | > 0.05 | Insign. |
| | S. Alb. | 1.87 | 0.5 | 2.01 | 0.3 | > 0.05 | Insign. |
| | PT | 19.95 | 6 | 17.73 | 2.1 | > 0.05 | Insign. |
| Renal Func. Test | S. Cr. | 2.35 | 1 | 2.39 | 0.8 | > 0.05 | Insign. |
| | BUN | 40.9 | 13.5 | 42.9 | 14.3 | > 0.05 | Insign. |
| | Cr. Clearance | 46.03 | 14.9 | 50.08 | 14.2 | > 0.05 | Insign. |
| Urinary Na | | 27.9 | 2.8 | 27.5 | 2.3 | > 0.05 | Insign. |
| S.Na | | 127.6 | 1.5 | 120.3 | 5.9 | < 0.01 | Highly sign. |
| S.K | | 4.53 | 0.5 | 4.53 | 1.2 | > 0.05 | Insign. |
| Blood picture | WBCs | 10.99 | 4.6 | 7.83 | 2.5 | < 0.05 | Sign. |
| | Hb | 9.3 | 1.2 | 9.99 | 1.3 | > 0.05 | Insign. |
| | Platelet | 77.9 | 25.1 | 92.7 | 23.3 | > 0.05 | Insign. |
| Ascitic fluid | Cell count | 1210 | 931 | 130 | 52.2 | < 0.01 | Highly sign. |
| | T. protein | 1.66 | 0.6 | 1.82 | 0.99 | > 0.05 | Insign. |
| | LDH | 487.8 | 293.3 | 175.5 | 62.5 | < 0.01 | Highly sign. |
| | Glucose | 105 | 22.1 | 181.3 | 56.6 | < 0.01 | Highly sign. |
| NO | Serum | 226.2 | 96.8 | 208.5 | 135.8 | < 0.05 | Sign. |
| | Ascites | 320.1 | 190.4 | 135.7 | 79.6 | < 0.05 | Sign. |

**Table (13):** Comparison between group A and group D as regards different variables.

| Variable | | Group A (n = 10) | | Group D (n = 10) | | P-value | Sign. |
|---|---|---|---|---|---|---|---|
| | | Mean | ± SD | Mean | ± SD | | |
| Liver Profile | ALT | 51.4 | 38.9 | 29.5 | 17 | > 0.05 | Insign. |
| | AST | 79.5 | 29.7 | 53.6 | 25.9 | > 0.05 | Insign. |
| | T. BIL | 4.46 | 3 | 2.21 | 1.1 | < 0.05 | Sign. |
| | D. BIL | 2.37 | 1.9 | 0.77 | 0.45 | < 0.05 | Sign. |
| | S. Alb. | 1.87 | 0.5 | 2.63 | 0.4 | < 0.01 | Highly sign. |
| | PT | 19.95 | 6 | 16.14 | 1.2 | < 0.05 | Sign. |
| Renal Func. Test | S. Cr. | 2.35 | 1 | 0.93 | 0.13 | < 0.01 | Highly sign. |
| | BUN | 40.9 | 13.5 | 13.3 | 3.9 | < 0.01 | Highly sign. |
| | Cr. Clearance | 46.03 | 14.9 | 103.69 | 11.2 | < 0.01 | Highly sign. |
| Urinary Na | | 27.9 | 2.8 | 62.5 | 5.5 | < 0.01 | Highly sign. |
| S.Na | | 127.6 | 1.5 | 134.7 | 4.9 | < 0.01 | Highly sign. |
| S.K | | 4.53 | 0.5 | 4 | 0.4 | < 0.05 | Sign. |
| Blood picture | WBCs | 10.99 | 4.6 | 5.31 | 1.1 | < 0.01 | Highly sign. |
| | Hb | 9.3 | 1.2 | 10.39 | 0.9 | < 0.05 | Sign. |
| | Platelet | 77.9 | 25.1 | 119.5 | 71.6 | < 0.01 | Highly sign. |
| Ascitic fluid | Cell count | 1210 | 931 | 68.2 | 30.0 | < 0.01 | Highly sign. |
| | T. protein | 1.66 | 0.6 | 1.99 | 1.9 | < 0.05 | Sign. |
| | LDH | 487.8 | 293.3 | 167.3 | 66.3 | < 0.01 | Highly sign. |
| | Glucose | 105 | 22.1 | 139.3 | 43 | < 0.05 | Sign. |
| NO | Serum | 226.2 | 96.8 | 114.4 | 43.7 | < 0.01 | Highly sign. |
| | Ascites | 320.1 | 190.4 | 99.7 | 8.9 | < 0.01 | Highly sign. |

**Table (14):** Comparison between group B and group C as regards different variables.

| Variable | | Group B (n = 10) | | Group C (n = 10) | | P-value | Sign. |
|---|---|---|---|---|---|---|---|
| | | Mean | ± SD | Mean | ± SD | | |
| Liver Profile | ALT | 90.2 | 103.6 | 28.8 | 7.1 | > 0.05 | Insign. |
| | AST | 135.6 | 92.2 | 63.8 | 27.7 | > 0.05 | Insign. |
| | T. BIL | 8.25 | 8.6 | 3.42 | 4 | > 0.05 | Insign. |
| | D. BIL | 4.49 | 5 | 1.55 | 2.4 | > 0.05 | Insign. |
| | S. Alb. | 2.2 | 0.5 | 2.01 | 0.3 | > 0.05 | Insign. |
| | PT | 17.53 | 4 | 17.73 | 2.1 | > 0.05 | Insign. |
| Renal Func. Test | S. Cr. | 0.89 | 0.3 | 2.39 | 0.8 | < 0.01 | Highly sign. |
| | BUN | 15.4 | 5.7 | 42.9 | 14.3 | < 0.01 | Highly sign. |
| | Cr. Clearance | 96.31 | 18.4 | 50.08 | 14.2 | < 0.01 | Highly sign. |
| Urinary Na | | 64.5 | 7.2 | 27.5 | 2.3 | < 0.01 | Highly sign. |
| S.Na | | 134.8 | 3.9 | 120.3 | 5.9 | < 0.01 | Highly sign. |
| S.K | | 4.63 | 0.6 | 4.53 | 1.2 | > 0.05 | Insign. |
| Blood picture | WBCs | 10.11 | 5.5 | 7.83 | 2.5 | > 0.05 | Insign. |
| | Hb | 10 | 1.6 | 9.99 | 1.3 | > 0.05 | Insign. |
| | Platelet | 92.4 | 20.7 | 92.7 | 23.3 | > 0.05 | Insign. |
| Ascitic fluid | Cell count | 628 | 519.5 | 130 | 52.2 | < 0.01 | Highly sign. |
| | T. protein | 1.35 | 0.8 | 1.82 | 0.99 | < 0.05 | Sign. |
| | LDH | 256 | 140.9 | 175.5 | 62.5 | < 0.05 | Sign. |
| | Glucose | 92.3 | 39.9 | 181.3 | 56.6 | < 0.01 | Highly sign. |
| NO | Serum | 134.7 | 85.6 | 208.5 | 135.8 | > 0.05 | Insign. |
| | Ascites | 191.2 | 113.3 | 135.7 | 79.6 | > 0.05 | Insign. |

**Table (15):** Comparison between group B and group D as regards different variables.

| Variable | | Group B (n = 10) | | Group D (n = 10) | | P-value | Sign. |
|---|---|---|---|---|---|---|---|
| | | Mean | ± SD | Mean | ± SD | | |
| Liver Profile | ALT | 90.2 | 103.6 | 29.5 | 17 | > 0.05 | Insign. |
| | AST | 135.6 | 92.2 | 53.6 | 25.9 | > 0.05 | Insign. |
| | T. BIL | 8.25 | 8.6 | 2.21 | 1.1 | < 0.05 | Sign. |
| | D. BIL | 4.49 | 5 | 0.77 | 0.45 | < 0.05 | Sign. |
| | S. Alb. | 2.2 | 0.5 | 2.63 | 0.4 | > 0.05 | Insign. |
| | PT | 17.53 | 4 | 16.14 | 1.2 | < 0.05 | Sign. |
| Renal Func. Test | S. Cr. | 0.89 | 0.3 | 0.93 | 0.13 | > 0.05 | Insign. |
| | BUN | 15.4 | 5.7 | 13.3 | 3.9 | > 0.05 | Insign. |
| | Cr. Clearance | 96.31 | 18.4 | 103.69 | 11.2 | > 0.05 | Insign. |
| Urinary Na | | 64.5 | 7.2 | 62.5 | 5.5 | > 0.05 | Insign. |
| S.Na | | 134.8 | 3.9 | 134.7 | 4.9 | > 0.05 | Insign. |
| S.K | | 4.63 | 0.6 | 4 | 0.4 | < 0.05 | Sign. |
| Blood picture | WBCs | 10.11 | 5.5 | 5.31 | 1.1 | < 0.01 | Highly sign. |
| | Hb | 10 | 1.6 | 10.39 | 0.9 | > 0.05 | Insign. |
| | Platelet | 92.4 | 20.7 | 119.5 | 71.6 | < 0.05 | Sign. |
| Ascitic fluid | Cell count | 628 | 519.5 | 68.2 | 30.0 | < 0.01 | Highly sign. |
| | T. protein | 1.35 | 0.8 | 1.99 | 1.9 | < 0.05 | Sign. |
| | LDH | 256 | 140.9 | 167.3 | 66.3 | < 0.05 | Sign. |
| | Glucose | 92.3 | 39.9 | 139.3 | 43 | < 0.05 | Sign. |
| NO | Serum | 134.7 | 85.6 | 114.4 | 43.7 | < 0.05 | Sign. |
| | Ascites | 191.2 | 113.3 | 99.7 | 8.9 | < 0.05 | Sign. |

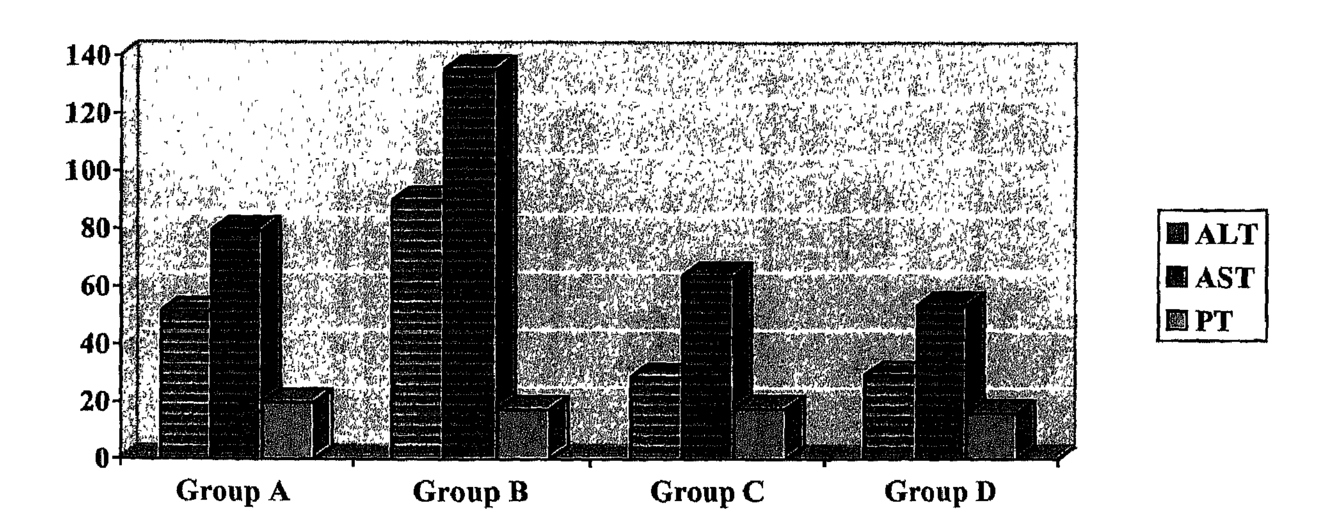
Table (16): Comparison between group C and group D as regards different variables.

| Variable | | Group C (n = 10) | | Group D (n = 10) | | P-value | Sign. |
|---|---|---|---|---|---|---|---|
| | | Mean | ± SD | Mean | ± SD | | |
| Liver Profile | ALT | 28.8 | 7.1 | 29.5 | 17 | > 0.05 | Insign. |
| | AST | 63.8 | 27.7 | 53.6 | 25.9 | > 0.05 | Insign. |
| | T. BIL | 3.42 | 4 | 2.21 | 1.1 | > 0.05 | Insign. |
| | D. BIL | 1.55 | 2.4 | 0.77 | 0.45 | > 0.05 | Insign. |
| | S. Alb. | 2.01 | 0.3 | 2.63 | 0.4 | < 0.05 | Sign. |
| | PT | 17.73 | 2.1 | 16.14 | 1.2 | < 0.05 | Sign. |
| Renal Func. Test | S. Cr. | 2.39 | 0.8 | 0.93 | 0.13 | < 0.01 | Highly sign. |
| | BUN | 42.9 | 14.3 | 13.3 | 3.9 | < 0.01 | Highly sign. |
| | Cr. Clearance | 50.08 | 14.2 | 103.69 | 11.2 | < 0.01 | Highly sign. |
| Urinary Na | | 27.5 | 2.3 | 62.5 | 5.5 | < 0.01 | Highly sign. |
| S.Na | | 120.3 | 5.9 | 134.7 | 4.9 | < 0.01 | Highly sign. |
| S.K | | 4.53 | 1.2 | 4 | 0.4 | > 0.05 | Insign. |
| Blood picture | WBCs | 7.83 | 2.5 | 5.31 | 1.1 | > 0.05 | Insign. |
| | Hb | 9.99 | 1.3 | 10.39 | 0.9 | > 0.05 | Insign. |
| | Platelet | 92.7 | 23.3 | 119.5 | 71.6 | > 0.05 | Insign. |
| Ascitic fluid | Cell count | 130 | 52.2 | 68.2 | 30.0 | > 0.05 | Insign. |
| | T. protein | 1.82 | 0.99 | 1.99 | 1.9 | > 0.05 | Insign. |
| | LDH | 175.5 | 62.5 | 167.3 | 66.3 | > 0.05 | Insign. |
| | Glucose | 181.3 | 56.6 | 139.3 | 43 | > 0.05 | Insign. |
| NO | Serum | 208.5 | 135.8 | 114.4 | 43.7 | < 0.05 | Sign. |
| | Ascites | 135.7 | 79.6 | 99.7 | 8.9 | > 0.05 | Insign. |

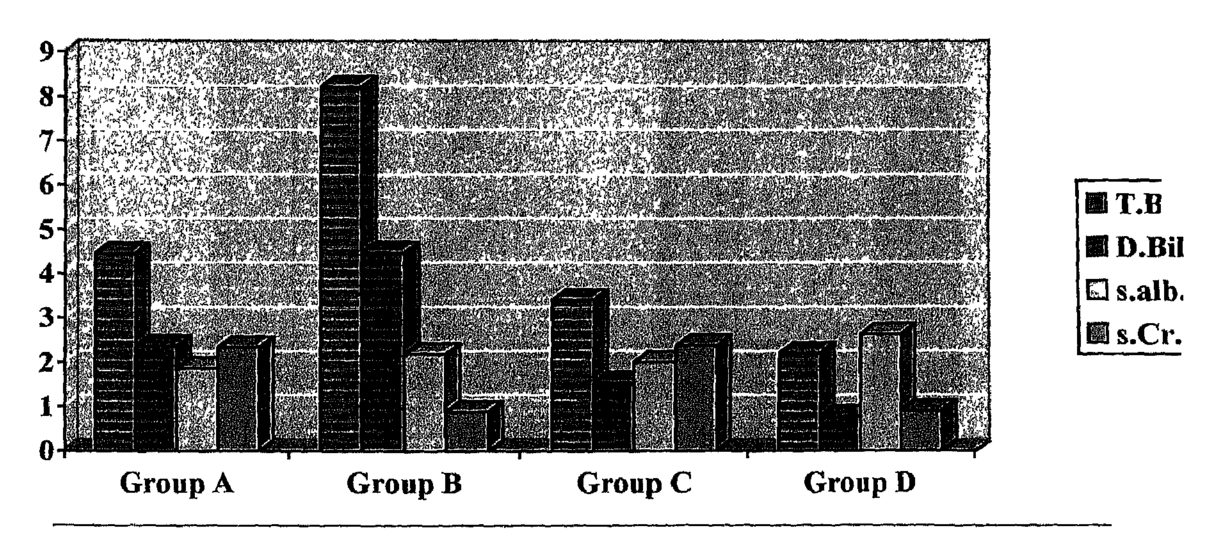
**Table (17):** Correlation between level of both serum and ascitic nitric oxide end products and different variables in the studied groups (in the patients as whole):

| Variable | Serum NO | | | Ascitic NO | | |
|---|---|---|---|---|---|---|
| | r | P | Sign. | r | P | Sign. |
| **AGE** | - 0.3 | > 0.05 | Insign. | - 0.18 | > 0.05 | Insign. |
| **ALT** | - 0.09 | > 0.05 | Insign. | - 0.09 | > 0.05 | Insign. |
| **AST** | - 0.004 | > 0.05 | Insign. | 0.04 | > 0.05 | Insign. |
| **T. BIL** | 0.23 | < 0.05 | *Sign. | 0.21 | < 0.05 | *Sign. |
| **D. BIL** | 0.12 | < 0.05 | *Sign. | 0.23 | < 0.05 | *Sign. |
| **PT** | 0.51 | < 0.01 | **Highly sign. | 0.43 | < 0.01 | **Highly sign. |
| **S. alb.** | - 0.62 | < 0.01 | **Highly sign. | - 0.53 | < 0.01 | **Highly sign. |
| **S. Cr.** | 0.21 | < 0.05 | *Sign. | 0.28 | < 0.05 | *Sign. |
| **BUN** | 0.22 | < 0.05 | *Sign. | 0.27 | < 0.05 | *Sign. |
| **Cr. Clearance** | - 0.28 | < 0.05 | *Sign. | - 0.27 | < 0.05 | *Sign. |
| **Urinary Na** | - 0.35 | < 0.05 | *Sign. | - 0.3 | < 0.05 | *Sign. |
| **S.Na** | - 0.2 | > 0.05 | Insign. | - 0.16 | > 0.05 | Insign. |
| **S.K** | - 0.05 | > 0.05 | Insign. | - 0.04 | > 0.05 | Insign. |
| **WBCs** | 0.33 | < 0.05 | *Sign. | 0.61 | < 0.01 | **Highly sign. |
| **Hb** | - 0.13 | > 0.05 | Insign. | - 0.11 | > 0.05 | Insign. |
| **Platelet** | - 0.19 | > 0.05 | Insign. | 0.21 | > 0.05 | Insign. |
| **Cell count** | 0.45 | < 0.01 | **Highly sign. | 0.40 | < 0.01 | **Highly sign. |
| **Total protein** | 0.03 | > 0.05 | Insign. | 0.09 | > 0.05 | Insign. |
| **LDH** | 0.56 | < 0.01 | **Highly sign. | 0.59 | < 0.01 | **Highly sign. |
| **Glucose** | - 0.03 | > 0.05 | Insign. | - 0.08 | > 0.05 | Insign. |

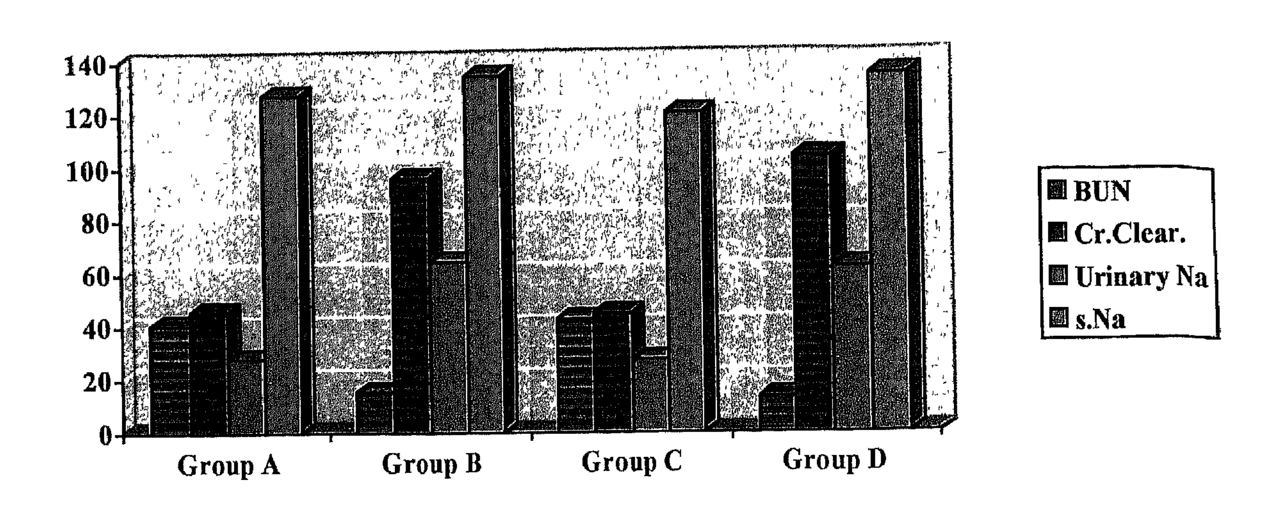
Graph (1): Comparison between the studied groups as regard ALT, AST and PT



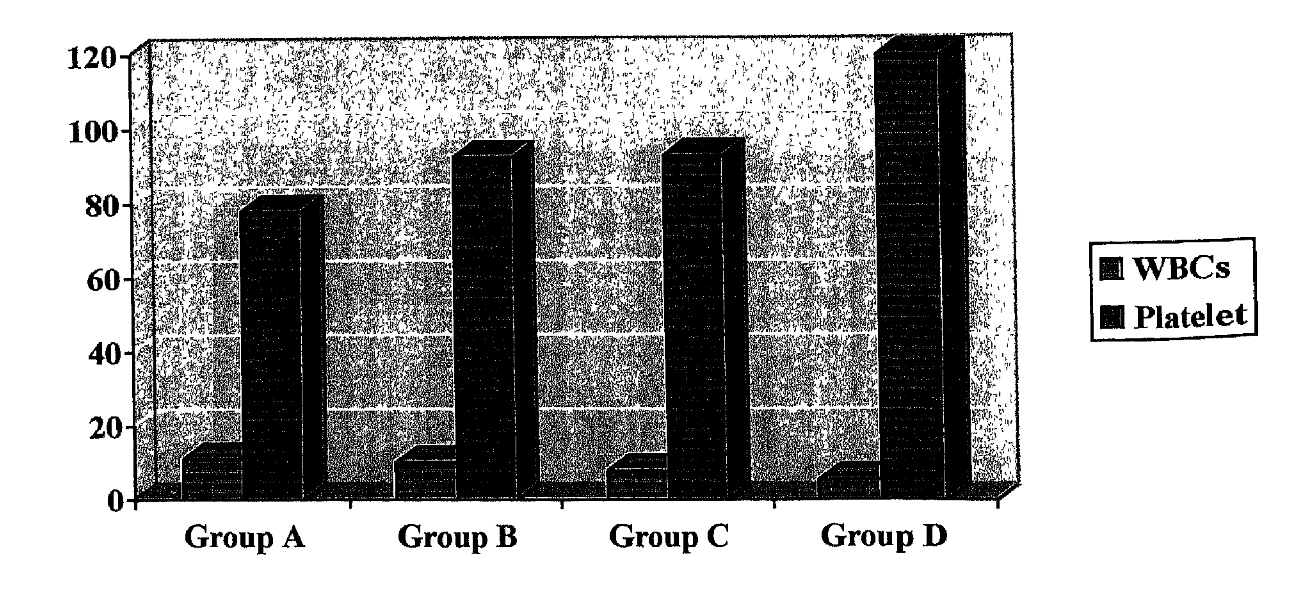

Graph (2): Comparison between the studied groups as regard Bil., s.alb. and s.Cr.



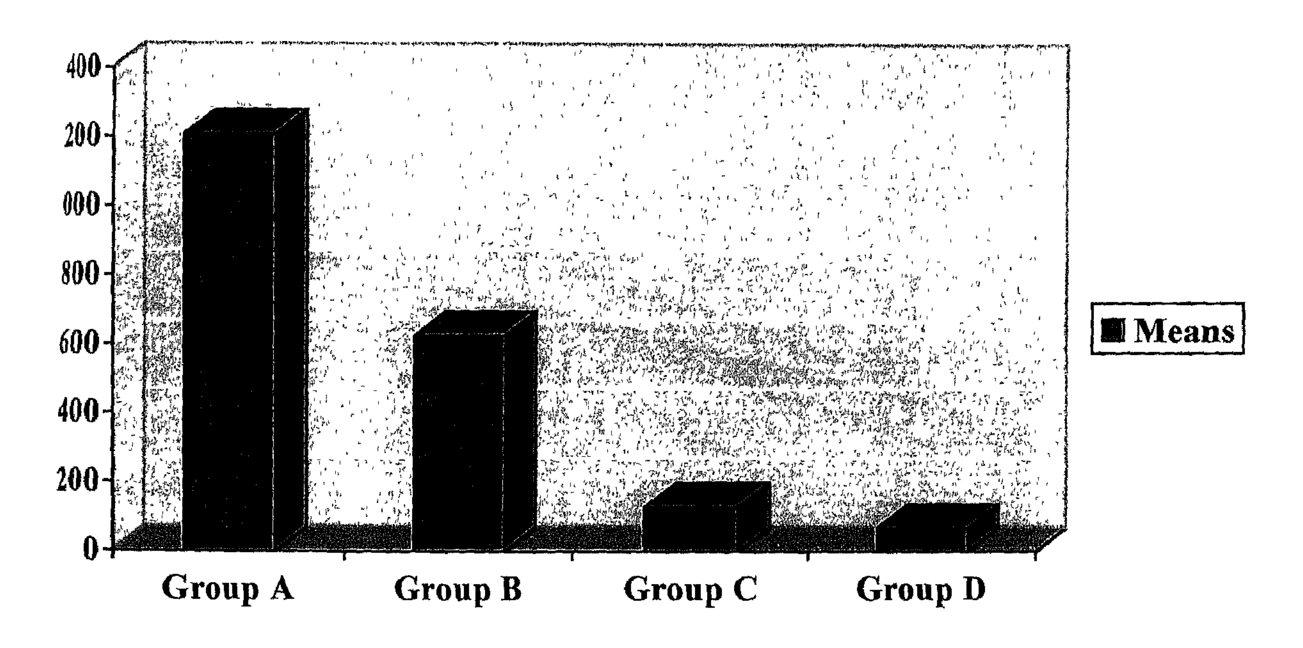
Graph (3): Comparison between the studied groups as regard BUN, Cr clearance, urinary Na and s.Na



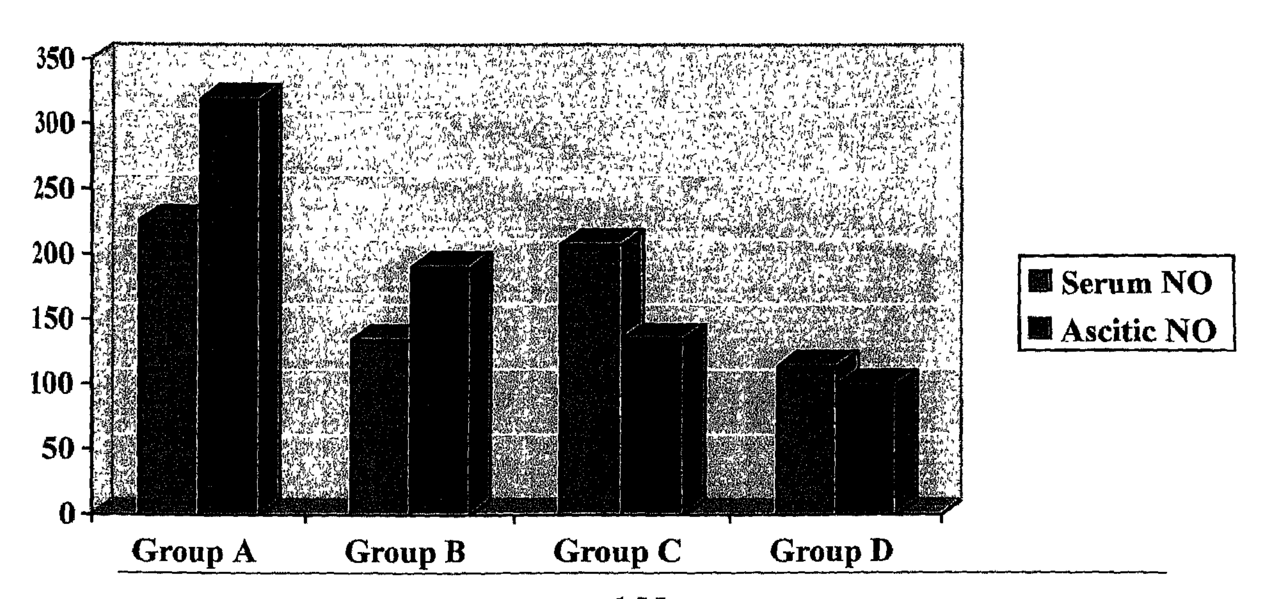

Graph (4): Comparison between the studied groups as regard WBCs and Platelet



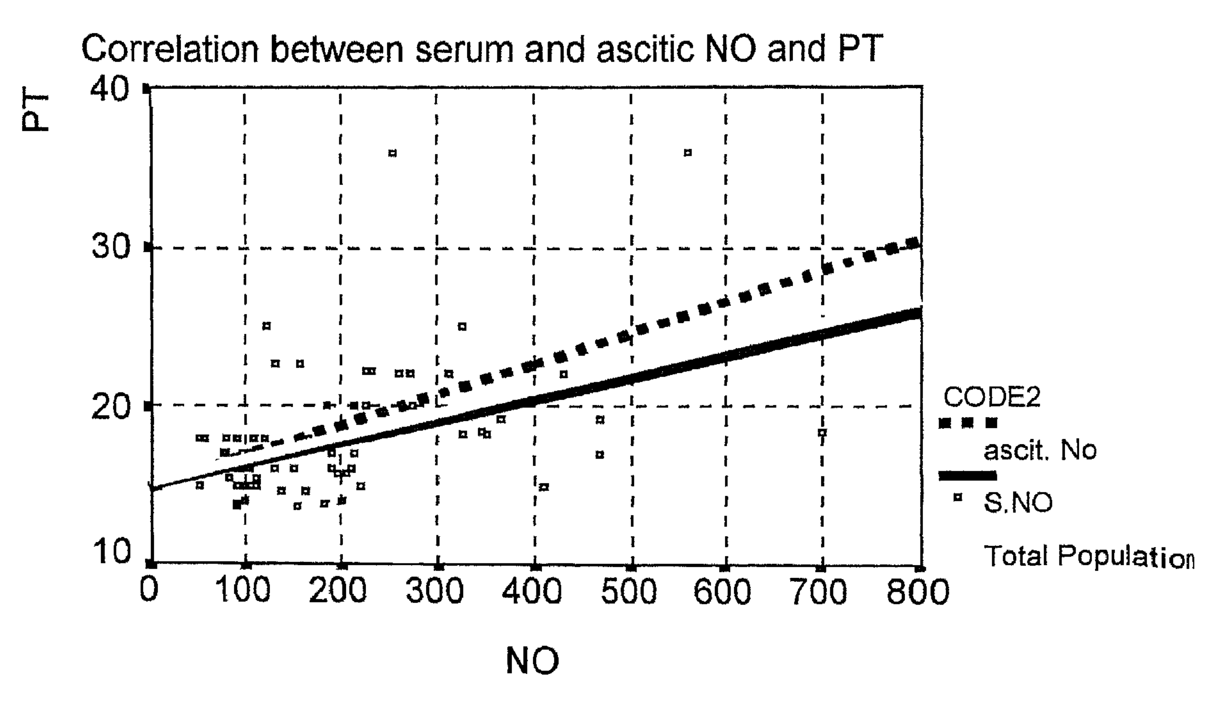
Graph (5): Comparison between the studied groups as regard ascetic fluid cell count

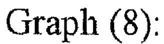



Graph (6): Comparison between the studied groups as regard Serum and Ascitic NO

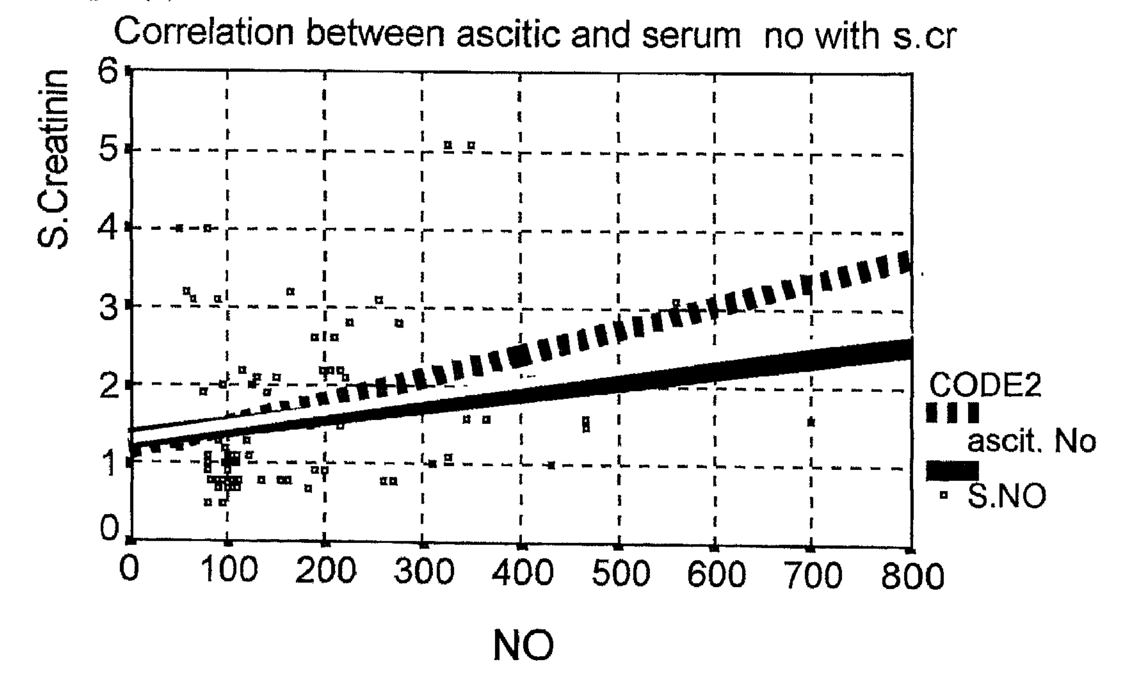


Graph (7):



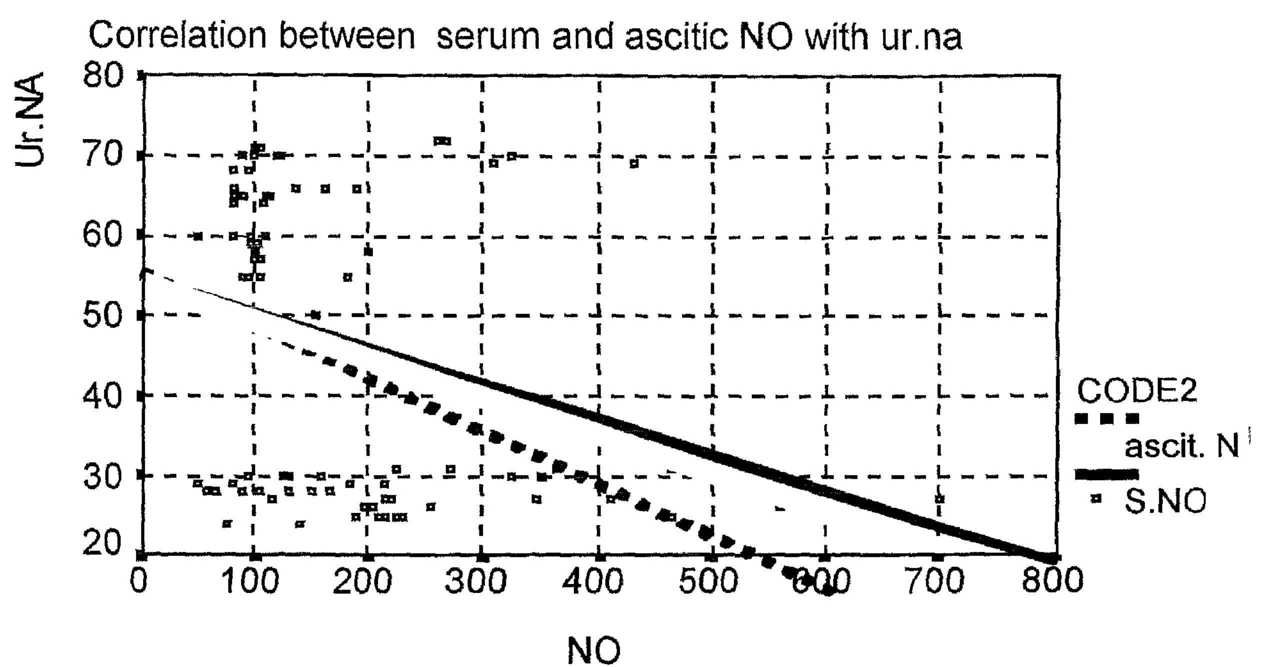



Graph (8):





Graph (9):




Graph (10):

Correlation between serum and ascitic NO with LDH

LDH

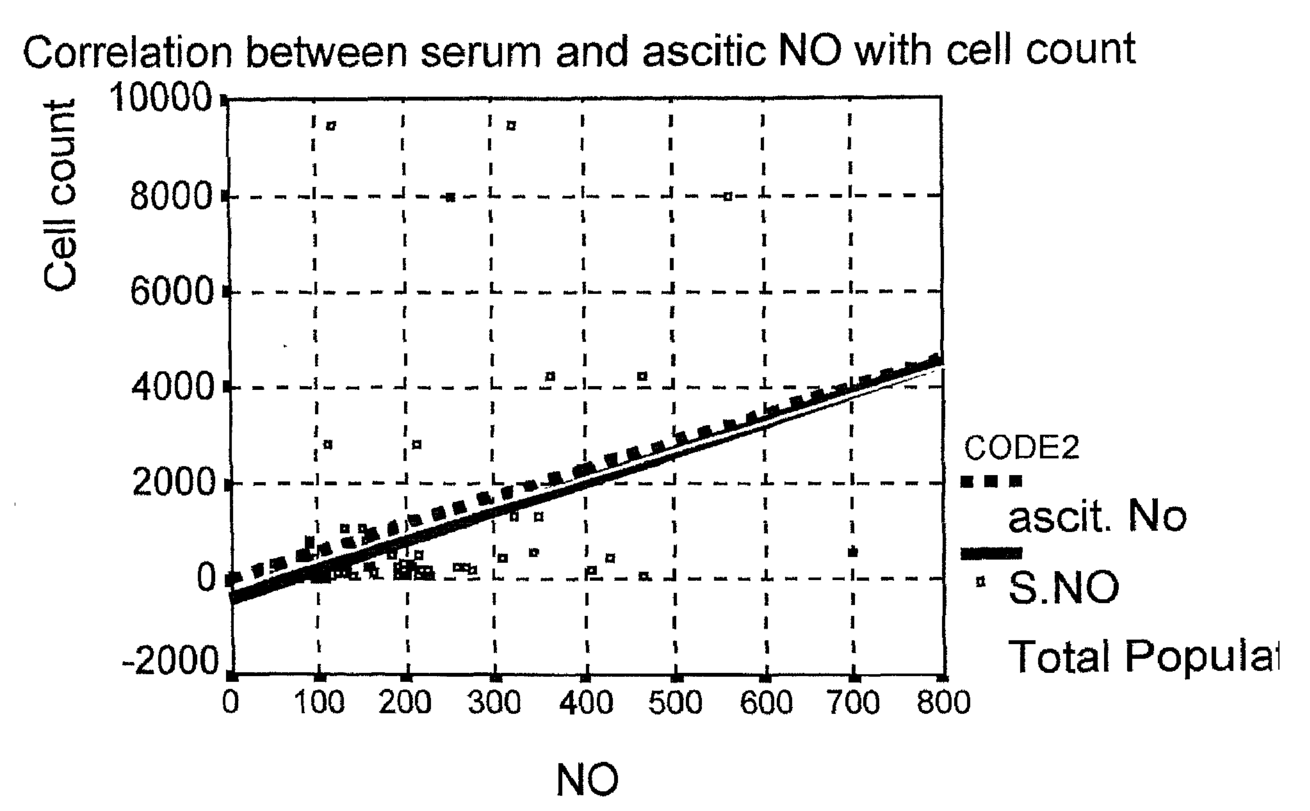
1200
1000
800
600
400
200
0

0 100 200 300 400 500 600 700 800

NO

CODE2
ascit. No
S.NO
Total Populati

Graph (11):



Correlation between serum and ascitic NO with cell count
Cell count
10000
8000
6000
4000
2000
0
-2000
0
100
200
300
400
500
600
700
800
NO
CODE2
ascit. No
S.NO
Total Populat


DISCUSSION

# DISCUSSION

Spontaneous bacterial peritonitis (SBP) is a frequent and severe complication in patients with liver cirrhosis and ascites, characterized by spontaneous infection of ascitic fluid that occurs in the absence of any intra-abdominal source of infection ***(Rimola et al., 2000)***.

It is generally accepted that SBP is a consequence of bacteremia, which is probably facilitated by depressed reticuloendothelial system phagocytic activity and serum complement deficiency ***(Soriano & Texido, 1991).***

Hepatorenal syndrome is a clinical condition that occurs in patients with advanced chronic liver disease, liver cell failure, and portal hypertension characterized by impaired renal function and marked abnormalities in the arterial circulation and activity of the endogenous vasoactive systems. In the kidney there is marked renal vasoconstriction that results in low glomerular filtration rate (GFR), whereas in the extrarenal circulation there is predominance of arterial vasodilatation, which results in reduction of total systemic vascular resistance and arterial hypotension ***(Arroyo et al., 1996)***.

Nitric oxide (NO) is a powerful vasodilating agent, that has been proposed to play a role in the pathogenesis of vasodilatation and hyperdynamic circulation associated with advanced cirrhosis ***(Laffi et al., 1995)***.

Patients with cirrhosis and spontaneous bacterial peritonitis have many of the features of the sepsis syndrome, with high levels of vasoactive cytokines ***(Navasa et al., 1998)***. This sepsis syndrome is associated with arterial vasodilatation, impairment of circulatory function, and activation of neurohumoral vasoconstrictor systems ***(Voerman et al., 1992)***.

Hepatorenal syndrome is the extreme expression of this circulatory dysfunction. Nitric oxide is thought to play a major role in the pathogenesis of this abnormality ***(Matsumoto et al., 1995)***. The vascular production of nitric oxide is stimulated by cytokines ***(Moncada et al., 1991)***.

In this study we found that abdominal pain was statistically higher in patients with SBP than patients with sterile ascites. In our study we found that fever was present in patients with SBP while it wasn't present in patients with sterile ascites. Also encephalopathy was present in patients with SBP while it wasn't present in patients with sterile ascites.

In a study done by ***Kaymakoglu et al., (1997)***, they found that most of the patients with SBP episodes presented with fever and abdominal pain. All patients except one had manifestations of hepatic encephalopathy. Previous reports stated that abdominal pain and fever were the most characteristic symptoms in patients with

SBP. However, non specific symptoms and signs such as vomiting, diarrhea, GIT hemorrhage, signs of hepatic encephalopathy shock or hypothermia might be present in a great number of patients ***(Hoefs et al., 1982).***

Moreover, some patients initially showed only mild deterioration in mental status, progressive kidney failure or refractoriness to diuretic therapy. However, SBP could be totally asymptomatic ***(Hoefs et al., 1982 and Pinzello et al., 1983).***

***Strauss & da-Costa (1998),*** in their study on 108 patients with acute hepatic encephalopathy, found mat 37 patients (34.7%) had associated bacterial infections. SBP was the most prevalent infection.

In this study there was statistically significant difference between the group of patients with SBP and patients with sterile ascites as regard serum albumin, total serum bilirubin and prothrombin time and this is agree with **Mansour et al., (1997)** who reported significantly higher levels of serum bilirubin and significantly lower levels of serum albumin and prothrombin activity in patients with infected ascites than in patients with sterile ascites. Their results were in accordance with **Hoefs et al., (1985)** who found a high prevalence of disturbances in serum bilirubin, albumin and prothrombin time among patients suffering from SBP.

with ***Runyon (1995)*** who showed that many patients with SBP had an elevated serum creatinine levels and in 21% this level was >2.1 mg/dl. ***Barnes et al., (1988)*** found that an elevated serum creatinine value was a poor prognostic sign and it might reflect acute tubular necrosis secondary to bacteremia or the functional renal impairment associated with severe hepatic dysfunction. Also ***Jimaénez et al., (1999)***, found that patients with SBP showed significantly higher serum creatinine and blood urea nitrogen than non infected patients.

It is also agree with the International Ascites Club's diagnostic criteria of hepatorenal syndrome, which state that major criteria include, chronic or acute liver disease with advanced hepatic failure and portal hypertension, and low glomerular filtration rate, as indicated by serum creatinine of > 1.5 mg/dl or 24 hour creatinine clearance < 40 ml/min. ***(Arroyo et al., 1996).***

In addition, urinary sodium was also significantly lower in group A (patients with SBP and HRS) and group C (patients with HRS) than in the group of patients with sterile ascites, this also agree with the criteria of diagnosis of hepatorenal syndrome. ***(Arroyo et al., 1996).***

Also this is agree with ***Sort et al., (1999)*** who state that, factors that have been associated with poor outcome in SBP include a serum albumin level of < 2.5 g/dl, serum creatinine level > 2.1 mg/dl, bilirubin > 8 mg /dl.

Serum bilirubin, particularly, was referred to as an important risk factor for development of SBP in cirrhotic patients during long term follow up by ***Andreu et al., (1993). Guarner et al., (1999)*** found that serum bilirubin > 3.2 mg/dl independently correlated with the risk of developing the first episode of SBP. So recent studies strongly supports the use of intravenous albumin in addition to antibiotics in treatment of spontaneous bacterial peritonitis, because intravenous infusion of human salt free albumin may reduce the rate of renal impairment and mortality ***(Sort et al., 1999).***

In this study we found that there was a prolonged prothrombin times in patients with SBP. This agrees with ***Novella et al., (1997)*** who conclude that PT is a predictive factor of a first nosocomial or community acquired episode of SBP in cirrhotic patients with ascites.

In this study we observed that, there was statistically significant difference among the studied groups as regard serum creatinine, BUN and creatinine clearance, with high levels in group A (patients with SBP with HRS) and group C (patients with HRS) when compared to the patients with sterile ascites. This is in accordance

In this study we found that serum sodium was significantly lower in group A (patients with SBP and HRS) and group C (patients with HRS) than in the group of patients with sterile ascites. This is due to the marked impairment of renal capacity to excrete free water leading to dilutional hyponatremia. It is agree ***Arroyo and Jimaénez (2000)*** who said that in patients with hepatorenal syndrome (serum creatinine concentration > 1.5 mg/dl) there was dilutional hyponatremia which is related to a reduced delivery of sodium to the ascending limb of the loop of Henle rather than to the hypersecretion of ADH present in these patients.

In this study we found that serum potassium significantly higher in group A (patients with SBP and HRS) and group C (patients with HRS) than in the group of patients with sterile ascites. This is explained by the marked impairment of renal function in patients with hepatorenal syndrome compared to other groups.

In this study, the white blood cell count in the peripheral blood was significantly higher in the group of patients with SBP than in patients with sterile ascites. This was documented by ***Hoefs et al., (1985), Almdal & Skinhoj (1987) and Toledo et al. (1993).***

***Lee et al. (1987)*** reported higher total white cell count in the peripheral blood of SBP patients than in patients with sterile ascites.

# Descriptive data of the studied groups:

| ENCEPH. | S.ALB | ALT | AST | T BIL | D BIL | PT | WBCs | PLT | Hb | S.Na | S.K | Kidney function tests | | | | Pelviabdominal U/S | | | | | Ascitic Fluid Bacteriology | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | S Creat | BUN | Creat. clearance | Urinary Na | PVD | LIVER | SPLEEN | ASCITIS | U/S KIDNEY | Cell type | Cell count | C&S |
| positive | 1.5 | 32 | 92 | 7.7 | 4.3 | 36 | 3.3 | 94 | 11 | 129 | 4.7 | 3.1 | 55 | 31.5 | 26 | 15 | liver cirrhosis | enlarged | positive | Normal | PMN | 900 | positive |
| positive | 2.4 | 14 | 55 | 5.3 | 2.5 | 22.7 | 7.1 | 35 | 11 | 129 | 4.5 | 1.5 | 20 | 61.1 | 30 | 15 | liver cirrhosis | enlarged | positive | Normal | PMN | 300 | positive |
| positive | 2.1 | 20 | 50 | 3 | 1.5 | 20 | 6.5 | 50 | 10 | 128 | 4.3 | 1.5 | 22 | 62.2 | 29 | 16 | liver cirrhosis | enlarged | positive | Normal | PMN | 500 | positive |
| positive | 0.9 | 20 | 53 | 6.5 | 4.6 | 18.3 | 18.6 | 41 | 9.3 | 127 | 3.7 | 5.1 | 57 | 18.5 | 30 | 15 | liver cirrhosis | enlarged | positive | Normal | PMN | 1150 | positive |
| positive | 1.5 | 67 | 96 | 10.7 | 5.8 | 19.2 | 14.2 | 90 | 9.8 | 128 | 4.1 | 1.6 | 30 | 61.1 | 31 | 16 | liver cirrhosis | enlarged | positive | Normal | PMN | 2600 | positive |
| negative | 1.6 | 44 | 82 | 5.4 | 2.2 | 18.5 | 13.3 | 92 | 9.1 | 127 | 4.3 | 1.6 | 33 | 61.4 | 27 | 17 | liver cirrhosis | enlarged | positive | Normal | PMN | 600 | positive |
| positive | 2.4 | 38 | 79 | 1.4 | 0.4 | 17 | 15.5 | 98 | 8 | 124 | 4.4 | 2.2 | 50 | 44.9 | 27 | 16 | liver cirrhosis | enlarged | positive | Normal | PMN | 940 | positive |
| negative | 2 | 40 | 78 | 2.1 | 0.9 | 16 | 11.5 | 94 | 9.1 | 128 | 4.6 | 2.1 | 46 | 48.6 | 28 | 15 | liver cirrhosis | enlarged | positive | Normal | PMN | 1820 | positive |
| positive | 2 | 118 | 60 | 2.1 | 0.7 | 16 | 10.1 | 90 | 8.1 | 127 | 5.4 | 2.6 | 50 | 37.6 | 25 | 18 | liver cirrhosis | enlarged | positive | Normal | PMN | 340 | positive |
| positive | 2.3 | 121 | 150 | 2.2 | 0.8 | 15.8 | 9.8 | 95 | 8.2 | 129 | 5.3 | 2.2 | 46 | 43.4 | 26 | 16 | liver cirrhosis | enlarged | positive | Normal | PMN | 2950 | positive |
| | 1.87 | 51.4 | 79.5 | 4.64 | 2.37 | 19.95 | 10.99 | 77.9 | 9.3 | 127.6 | 4.53 | 2.35 | 40.9 | 47.03 | 27.9 | 15.9 | | | | | | 1210 | |
| | 0.5 | 38.9 | 29.7 | 3 | 1.9 | 6 | 4.6 | 25.1 | 1.2 | 1.5 | 0.5 | 1 | 13.5 | 14.9 | 2.8 | 1 | | | | | | 931 | |
| positive | 1.2 | 45 | 99 | 10.8 | 5.5 | 25 | 5.6 | 66 | 10 | 131 | 4.8 | 1.1 | 21 | 98.9 | 70 | 14 | liver cirrhosis | enlarged | positive | Normal | PMN | 2150 | positive |
| positive | 1.9 | 30 | 91 | 4.1 | 2.1 | 22 | 13.5 | 90 | 11 | 132 | 5.4 | 1 | 15 | 104 | 69 | 15 | liver cirrhosis | enlarged | positive | Normal | PMN | 450 | positive |
| negative | 2.9 | 34 | 75 | 0.7 | 0.2 | 14.6 | 7.8 | 106 | 13 | 133 | 4 | 0.8 | 10 | 113.8 | 66 | 14 | liver cirrhosis | enlarged | positive | Normal | PMN | 300 | positive |
| negative | 2.5 | 90 | 210 | 24.2 | 13.5 | 22.1 | 22.1 | 105 | 9.4 | 133 | 5.1 | 0.8 | 10 | 111.8 | 72 | 23 | liver cirrhosis | enlarged | positive | Normal | PMN | 370 | positive |
| negative | 2.1 | 26 | 32 | 1.3 | 0.4 | 13.7 | 3.7 | 75 | 11 | 130 | 4 | 0.8 | 9 | 72 | 50 | 16 | liver cirrhosis | enlarged | positive | Normal | PMN | 760 | positive |
| negative | 2 | 34 | 42 | 1.4 | 0.5 | 13.9 | 4 | 80 | 10 | 134 | 4.1 | 0.7 | 8 | 75 | 55 | 16 | liver cirrhosis | enlarged | positive | Normal | PMN | 622 | positive |
| positive | 2.5 | 150 | 250 | 3 | 1.5 | 18 | 8.9 | 75 | 8.5 | 136 | 5.1 | 1.3 | 21 | 75.3 | 70 | 17 | liver cirrhosis | enlarged | positive | Normal | PMN | 330 | positive |
| negative | 2.7 | 59 | 125 | 18.8 | 10.8 | 16 | 12.5 | 137 | 11 | 142 | 4.1 | 0.5 | 18 | 117 | 68 | 16 | liver cirrhosis | enlarged | positive | Normal | PMN | 478 | positive |
| negative | 2.5 | 69 | 120 | 16.1 | 9.5 | 15 | 13.1 | 100 | 10 | 140 | 4.5 | 0.7 | 20 | 115 | 65 | 15 | liver cirrhosis | enlarged | positive | Normal | PMN | 460 | positive |
| positive | 2.9 | 365 | 312 | 2.1 | 0.9 | 15 | 9.9 | 90 | 7 | 137 | 5.2 | 1.2 | 22 | 83.3 | 60 | 14 | liver cirrhosis | enlarged | positive | Normal | PMN | 360 | positive |
| | 2.2 | 90.2 | 136 | 8.25 | 4.49 | 17.53 | 10.11 | 92.4 | 10 | 134.8 | 46.3 | 0.89 | 15.4 | 96.61 | 64.5 | 16 | | | | | | 628 | |
| | 0.5 | 104 | 92.2 | 8.6 | 5 | 4 | 5.5 | 20.7 | 1.6 | 3.9 | 0.6 | 0.3 | 5.7 | 18.4 | 7.2 | 2.7 | | | | | | 519.5 | |
| negative | 2.6 | 23 | 46 | 1.2 | 0.4 | 17 | 6.5 | 103 | 13 | 126 | 3.9 | 2 | 41 | 46.7 | 30 | 14 | liver cirrhosis | enlarged | positive | Normal | PMN | 125 | negative |
| positive | 2.1 | 42 | 69 | 2.3 | 0.6 | 17 | 7.9 | 50 | 8.6 | 124 | 3.2 | 1.5 | 21 | 68.9 | 25 | 16 | liver cirrhosis | enlarged | positive | Normal | PMN | 75 | negative |
| positive | 1.5 | 24 | 36 | 2.3 | 1.1 | 14.9 | 9.3 | 120 | 9.8 | 127 | 4.2 | 2.1 | 45 | 44.4 | 27 | 15 | liver cirrhosis | enlarged | positive | Normal | PMN | 230 | negative |
| positive | 1.7 | 26 | 117 | 2.4 | 1.2 | 20.1 | 9.5 | 72 | 11 | 111 | 4 | 2.8 | 31 | 35.7 | 31 | 15 | liver cirrhosis | enlarged | positive | Normal | PMN | 180 | negative |
| negative | 2.1 | 34 | 109 | 2.3 | 1.3 | 17 | 6 | 91 | 12 | 128 | 4.1 | 1.6 | 26 | 61.1 | 28 | 15 | liver cirrhosis | enlarged | positive | Normal | PMN | 175 | negative |
| positive | 2.2 | 16 | 57 | 14.7 | 8.2 | 18 | 6.2 | 80 | 10 | 119 | 7.7 | 4 | 66 | 27.7 | 29 | 16 | liver cirrhosis | enlarged | positive | Normal | PMN | 100 | negative |
| negative | 2.1 | 28 | 48 | 2.4 | 0.7 | 17 | 5.9 | 100 | 9.7 | 120 | 4.8 | 1.9 | 40 | 54.9 | 24 | 15 | liver cirrhosis | enlarged | positive | Normal | PMN | 70 | negative |
| negative | 2.3 | 32 | 64 | 2.9 | 1.1 | 22.3 | 13.9 | 82 | 9.6 | 119 | 5 | 1.7 | 46 | 51.5 | 25 | 15 | liver cirrhosis | enlarged | positive | Normal | PMN | 80 | negative |
| negative | 1.7 | 31 | 47 | 2.5 | 0.5 | 18 | 6.7 | 130 | 8.8 | 114 | 4.1 | 3.2 | 58 | 29.8 | 28 | 17 | liver cirrhosis | enlarged | positive | Normal | PMN | 130 | negative |
| negative | 1.8 | 32 | 45 | 1.2 | 0.4 | 16 | 6.4 | 99 | 8.5 | 115 | 13 | 3.1 | 55 | 30.1 | 28 | 16 | liver cirrhosis | enlarged | positive | Normal | PMN | 135 | negative |
| | 2.01 | 28.8 | 63.8 | 3.42 | 1.55 | 17.73 | 7.83 | 92.7 | 10 | 120.3 | 4.53 | 2.39 | 42.9 | 45.08 | 27.5 | 15.4 | | | | | | 130 | |
| | 0.3 | 7.1 | 27.7 | 4 | 2.4 | 2.1 | 2.5 | 23.3 | 1.3 | 5.9 | 1.2 | 0.8 | | 14.2 | 2.3 | 0.8 | | | | | | 52.2 | |
| negative | 2.7 | 29 | 55 | 3.1 | 1 | 15 | 3.5 | 110 | 11 | 139 | 4.5 | 1.1 | 16 | 92.9 | 57 | 15 | liver cirrhosis | enlarged | positive | Normal | PMN | 70 | negative |
| negative | 2.6 | 28 | 34 | 1.8 | 0.6 | 17 | 6.1 | 32 | 9.2 | 124 | 4.4 | 1 | 10 | 100.1 | 60 | 18 | liver cirrhosis | enlarged | positive | Normal | PMN | 50 | negative |
| negative | 2.9 | 32 | 57 | 2.9 | 0.9 | 14 | 3.7 | 125 | 11 | 140 | 4.3 | 0.9 | 15 | 111.7 | 58 | 15 | liver cirrhosis | enlarged | positive | Normal | PMN | 82 | negative |
| negative | 3 | 74 | 124 | 1.7 | 0.8 | 16 | 5.6 | 104 | 11 | 134 | 3.5 | 1 | 16 | 93.3 | 70 | 16 | liver cirrhosis | enlarged | positive | Normal | PMN | 20 | negative |
| negative | 3 | 21 | 40 | 1.1 | 0.4 | 16 | 7.1 | 300 | 9.6 | 137 | 4 | 0.7 | 11 | 119 | 71 | 14 | liver cirrhosis | enlarged | positive | Normal | PMN | 100 | negative |
| negative | 2.5 | 14 | 39 | 2.1 | 0.6 | 15.4 | 5 | 159 | 11 | 133 | 3.5 | 0.8 | 8 | 120 | 65 | 16 | liver cirrhosis | enlarged | positive | Normal | PMN | 60 | negative |
| negative | 1.5 | 17 | 55 | 4.8 | 1.9 | 17 | 5.3 | 70 | 8.5 | 134 | 3.8 | 0.9 | 17 | 104.6 | 66 | 15 | liver cirrhosis | enlarged | positive | Normal | PMN | 70 | negative |
| negative | 2.5 | 35 | 40 | 2 | 0.7 | 16 | 6.5 | 100 | 11 | 130 | 3.6 | 1 | 10 | 95.8 | 59 | 15 | liver cirrhosis | enlarged | positive | Normal | PMN | 130 | negative |
| negative | 3 | 22 | 44 | 1.1 | 0.4 | 17 | 5.2 | 107 | 11 | 138 | 4.2 | 0.8 | 10 | 110.6 | 55 | 14 | liver cirrhosis | enlarged | positive | Normal | PMN | 50 | negative |
| negative | 2.6 | 23 | 48 | 1.5 | 0.4 | 18 | 5.1 | 88 | 11 | 138 | 4.2 | 1.1 | 20 | 88.9 | 64 | 14 | liver cirrhosis | enlarged | positive | Normal | PMN | 50 | negative |
| | 2.63 | 29.5 | 53.6 | 2.21 | 0.77 | 16.14 | 5.31 | 120 | 10 | 134.7 | 4 | 0.93 | 13.3 | 103.69 | 62.5 | 15.2 | | | | | | 68.2 | |
| | 0.4 | 17 | 25.9 | 1.1 | 0.45 | 1.2 | 1.1 | 71.6 | 0.9 | 4.9 | 0.4 | 0.2 | | 11.2 | 5.5 | 1.2 | | | | | | 30.6 | |

***Kaymakoglu et al. (1997)*** reported significant increase in the peripheral WBC count in patients with SBP more than patients with sterile ascites.

In this study we found that platelet count was significantly lower in the group of patients with SBP than in patients with sterile ascites, this agrees with ***Guarner et al., (1999).***

In this study we found that ascitic fluid total proteins was significantly lower in the group of patients with SBP than in patients with sterile ascites. This is agree with ***Guarner et al., (1999)*** who conclude that cirrhotic patients with low ascitic fluid total protein levels (< 1 g/dl) and high bilirubin level and /or low platelet count are at high risk of developing a first episode of SBP during long term follow up.

These results were matched with ***Kaymakoglu et al., (1997)*** who reported that ascitic fluid total proteins were lower in patients with SBP than patient with sterile cirrhotic ascites and to ***Runyon et al., (1986)*** who demonstrated that patients with low ascitic fluid total proteins (<1 g/dl) had a 10-fold higher incidence of SBP than those with high ascitic fluid total protein content (> 1 g/dl). Moreover, in a long-term study carried out by ***Andreu et al. (1993),*** low ascitic fluid total protein level (< 1 g/dl) was found to be the most important predisposing factor for developing the first episode of SBP.

The opsonic activity of the ascitic fluid has been reported to be directly related to the total protein concentration of ascitic fluid ***(Runyon et al., 1985).***

In this study we found that ascitic fluid LDH level was significantly higher in the group of patients with SBP than in patients with sterile ascites. This can be explained by the fact that LDH is released by the disintegrating neutrophils and its concentration increases if the PMN count rises highly enough ***(Runyon & Hoefs, 1984a).***

In this study we found that ascitic fluid glucose level was significantly lower in the group of patients with SBP than in patients with sterile ascites. This may be explained by the fact that glucose is consumed by ascitic fluid white cells and bacteria ***(Akriviadis & Runyon 1990).***

In this study we observe that serum and ascitic nitric oxide end products level was significantly higher in the group of patients with SBP than in patients with sterile ascites. This agrees with ***Bories et al., (1997)*** who showed that SBP in cirrhotic patients was accompanied by an increased endogenous NO production, which was detected by an increase in concentrations of nitrate in serum and ascitic fluid. This overproduction may contribute to maintaining splanchnic vasodilatation and hyperdynamic circulation.

***Vallance and Moncada (1991)*** have hypothesized that endotoxemia might induce the synthesis and release of NO by iNOS, either directly or indirectly via cytokines, and this might therefore account for the hyperdynamic circulation, associated with cirrhosis. This is supported by the finding of ***Jimaénez, (1999)*** who said that cirrhotic patients with SBP had a higher NOx concentration than patients without peritonitis.

Furthermore NO production may have an effect on mucosal barrier function, thus favoring bacterial translocation and recurrence of SBP in cirrhotic patients ***(Salzman et al., 1995).***

In this study we observed that serum and ascitic nitric oxide end products level was significantly higher in the group of patients with HRS than in patients with ascites and normal renal function. This is matched with ***Mackenzie et al., (1996)*** who suggested that renal function has a significant effect on NOx concentration.

Also ***Bories et al., (1997)*** said that nitrate, being a small ion, is distributed in the total extracellular volume. Its hall-life is mainly determined by renal mechanisms, through filtration by the kidney and reabsorption in the tubules. These factors are important in determining the increase or decrease in plasma levels following variation in its synthesis rate.

It is also agrees with ***Guarner et al., (1993)*** who stated that, levels of serum NOx were higher in patients with functional kidney failure. Moreover endotoxemia was significantly more severe in patients with functional kidney failure.

In this study we found that the highest levels of serum and ascitic nitric oxide end products were present in the group of patients with SBP and renal impairment. This agrees with ***Guarner et al., (1993)*** who found that NO level correlate with the degree of endotoxemia; values were particularly increased in patients with ascites and functional kidney failure.

In this study there was a statistically highly significant positive correlation between both serum and ascitic nitric oxide end products and prothrombin time. This agrees with ***Garcia-Tsao et al., (1998)*** who said that among patients with SBP those with high NOx levels appear to have a more advanced liver disease as evidenced by prolonged prothrombin time.

In this study there was a statistically highly significant negative correlation between both serum and ascitic nitric oxide end products and serum albumin. ***Curran et al. (1990) & Curran et al (1991)*** explained this negative correlation, who stated that NO is considered a mediator of decreased hepatocyte protein synthesis

mainly albumin. This inhibition is produced directly by NO or via stimulation of kupffer cells to produce cytokines as TNF & IL-1.

In this study there was a significant positive correlation between both serum and ascitic nitric oxide end products and serum creatinine. It is in accordance with ***Mackenzie et al., (1996)*** who suggested that the correlation between NOx and serum creatinine was strong and highly significant, thus alternation of renal functions that are sufficient to be reflected in changes of creatinine concentration will be accompanied by changes in NOx levels.

In this study there was a significant positive correlation between both serum and ascitic nitric oxide end products and BUN creatinine clearance. This is explained by ***Campillo et al., (1996),*** who said that patients with ascites and renal impairment have high level of NOx.

In this study there was a statistically significant negative correlation between both serum and ascitic nitric oxide end products and urinary sodium. It is in accordance with ***Guarner et al., (1993)*** who foundout that urinary sodium excretion was inversely related to NOx levels, suggesting that high serum NOx levels are associated with marked renal retention of sodium.

***Claria et al., (1992)*** observed that administration of N-nitro-L-arginine, a competitive inhibitor of NO biosynthesis, to cirrhotic rats

increased mean arterial pressure, glomerular filtration rate and sodium urinary excretion.

In this study there was a significant positive correlation between serum nitric oxide end products and white blood cell count, while there was a highly significant positive correlation between ascitic nitric oxide end products and white blood cell count. This is matched with ***Morales-Ruiz et al., (1997)*** who said that peripheral leukocytes of patients with cirrhosis show greater NOS activity and more nitrate.

Also ***Laffi et al., (1995)*** had reported a higher iNOS activity in neutrophils and monocytes in patients with advanced liver cirrhosis, ascites, hyperdynamic circulation and endotoxemia.

In this study there was a highly significant positive correlation between both serum and ascitic nitric oxide end products and ascitic lactic dehydrogenase enzyme. This positive correlation may be explained by the fact that both LDH and NOx are released by disintegrated neutrophils.

In this study we found that there is highly significant positive correlation between serum and ascitic NOx. This is in accordance to ***Garcia-Tsao et al., (1998)***.

# SUMMARY

# SUMMARY

Patients with cirrhosis and spontaneous bacterial peritonitis have high levels of vasoactive cytokines and associated with arterial vasodilatation, impairment of circulatory function, and activation of neurohumoral vasoconstrictor systems ***(Sort et al., 1999)***.

Hepatorenal syndrome is the extreme expression of this circulatory dysfunction. Nitric oxide is thought to play a major role in the pathogenesis of these abnormalities because cytokines stimulate the vascular production of NO ***(Matsumoto et al., 1995).***

This study was carried on four groups of patients with liver cirrhosis; Group (A) included 10 patients with diagnosed SBP with renal impairment, Group (B) included 10 patients with SBP with normal renal function, Group (C) included 10 patients with sterile ascitic fluid with renal impairment and Group (D) included 10 patients with sterile ascitic fluid with normal renal function.

Full history, thorough clinical examination and laboratory investigations including urine analysis, blood picture, liver function tests, kidney function tests, chemical & bacteriological examination

of the ascitic fluid were carried out. Pelviabdominal ultrasonography was also done.

Nitrite and nitrate were measured in the serum and ascitic fluid of all the studied groups, as an end products of Nitric Oxide.

The aim of this work is to estimate the serum and ascitic level of NO in patients with liver cirrhosis and ascites complicated with SBP with and without HRS, and in patients with HRS, and compare the results with patients with sterile ascites and with normal kidney function as a control group, to find out its possible relation to renal impairment.

Our results revealed that level of nitric oxide end products was higher in patients with SBP and HRS than in patients with sterile ascites and normal renal function.

A highly significant positive correlation was found between both serum and ascitic nitric oxide end products and prothrombin time, while a highly significant negative correlation was found between both serum and ascitic nitric oxide end products and serum albumin.

A statistically significant positive correlation was found between both serum and ascitic nitric oxide end products and serum creatinine, BUN and creatinine clearance. While a statistically

significant negative correlation was found between both serum and ascitic nitric oxide end products and urinary sodium.

Also there was a positive correlation between both serum NO and ascitic NO.

# CONCLUSION

# CONCLUSION

Serum nitric oxide level is higher in cirrhotic patients with SBP and HRS than patients with sterile ascites and normal renal function. So nitric oxide derived from vascular endothelium which is a potent vasodilator, may play a key role in the circulatory dysfunction and consequently the development of HRS.

Levels of nitrite and nitrate were increased in patients with functional renal failure, this may be due to diminished renal excretion of nitrite and nitrate. These results suggest that renal function has a significant effect on NO concentrations.

# RECOMENDATIONS

# RECOMMENDATIONS

- **The following are recommended:**

1) Early diagnosis of spontaneous bacterial peritonitis, a diagnostic paracentesis should be performed for any cirrhotic patient with ascites, who developed clinical deterioration specially, unexplained hepatic encephalopathy.

2) It is better to inoculate the ascitic fluid in the blood cultures at bedside instead of the conventional culture method for rapid detection of causative organisms and to avoid the possibility of death of the organisms in the sample's way to the laboratory.

3) Awareness of the risk of renal failure and avoidance of nephrotoxic agents and of brisk reductions in effective circulating volume are important for prevention of hepatorenal syndrome.

4) Major and minor criteria for the diagnosis of hepatorenal syndrome should be applied on every cirrhotic patient.

5) Increased knowledge about mediators and synthesis of specific agonist and antagonists involved in hepatorenal syndrome may add promising treatment options in the near future.

6) As nitric oxide is highly increased in spontaneous bacterial peritonitis and hepatorenal syndrome: This should stimulate extensive prospective study for the factors modifying its action.

7) Role of nitric oxide antagonist in treatment of hyperdynamic state of liver cirrhosis and hepatorenal syndrome should be studied in prospective controlled trials.

8) Follow up study on the effects of NO on albumen synthesis & clotting factor.

9) Follow up study on the effects of endotoxemia on NO synthesis.

10) Attempts to improve renal function in hepatorenal syndrome by agonists, antagonists of vasoactive substances.

11) Also we recommend the use of prophylactic antibiotics to decrease the incidence of SBP in patients with cirrhosis and ascites. Prophylactic antibiotic is recommended in the following categories of patients: (A) Patients with decompensated liver cirrhosis and ascites after a first episode of SBP, (B) Patients with liver cirrhosis and ascites variceal bleeding and (C) Patients with liver cirrhosis who will undergo procedures e.g. ERCP.

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# ARABIC SUMMARY

– **المجموعة الثالثة** : تضم ١٠ مرضى بالتليف الكبدي و الاستسقاء ولا يعانون من الالتهاب البريتوني البكتيري التلقائي و الفشل الكبدي الكلوي.

– **المجموعة الرابعة** : تضم ١٠ مرضى بالتليف الكبدي و الاستسقاء ولا يعانون الالتهاب البريتوني البكتيري التلقائي مع وظائف كلى طبيعية.

_ و قد تم الآتي :

١) أخذ التاريخ المرضي كاملاً و عمل فحص إكلينيكي كامل للمرضى.

٢) تحليل وظائف الكبد.

٣) تحليل وظائف الكلى.

٤) قياس مستوى الصوديوم و البوتاسيوم بالدم.

٥) قياس مستوى الصوديوم في البول (٢٤ ساعة).

٦) عينات استسقاء لعمل: تحليل كيميائي و تحليل بكتيري.

٧) قياس مستوى أكسيد النيتريك في الدم و سائل الاستسقاء.

٨) أشعة تليفزيونية على البطن و الحوض.

٩) تحليل بول كامل.

و بالدراسة وجد أن مستوى أكسيد النيتريك في مرضى الالتهاب البريتوني البكتيري التلقائي و الفشل الكلوي الكبدي أعلى من مستوى أكسيد النيتريك في مرضى التليف الكبدي و الاستسقاء بدون الالتهاب البريتوني البكتيري التلقائي مع وظائف كلى طبيعية.

و قد وجدت علاقة عكسية بين مستوى أكسيد النيتريك و مستوى الزلال في الدم، بينما وجدت علاقة طردية بين مستوى أكسيد النيتريك ومستوى الكرياتينين بالدم .

أيضا وجدت علاقة طردية بين مستوى أكسيد النيتريك في الدم و مستواه في سائل الاستسقاء.

# الملخص العربي

إن معدل حدوث الالتهابات البكتيرية في مرضى التليف الكبدي مرتفع . ويعتبر الالتهاب البريتوني البكتيري التلقائي من أكثر الالتهابات البكتيرية حدوثا في مرضى التليف الكبدي و الاستسقاء .

ينتج أكسيد النيتريك بعدة أنواع من الخلايا . و يعتبر أكسيد النيتريك عاملا هاما في انبساط الأوعية الدموية ، و يعتبر أيضا وسيطا هاما في كثير من تفاعلات الجسم ضد الالتهابات . مستوى أكسيد النيتريك في مرضى التليف الكبدي له علاقة بزيادة كمية الدم المدفوعة من القلب و زيادة سرعة خفقان القلب ، و أيضا انخفاض ضغط الدم .

إن الالتهاب البريتوني البكتيري التلقائي في مرضى التليف الكبدي يكون مصحوب بارتفاع في نسبة أكسيد النيتريك. كما لوحظ ارتفاع معدل حدوث اضطرابات وظائف الكلى في مرضى الالتهاب البريتوني البكتيري التلقائي .

و تهدف هذه الدراسة إلى تحديد مستوى النترات كمنتج نهائي لأكسيد النيتريك في كل من عينة الدم و عينة الاستسقاء في مرضى التليف الكبدي مع الالتهاب البريتوني البكتيري التلقائي ، و ذلك لتحديد علاقته باضطرابات وظائف الكلى في هؤلاء المرضى.

وقد أجريت هذه الدراسة على ٤٠ مريضا من مرضى التليف الكبدي. و قد تم تقسيم المرضى إلى ٤ مجموعات:

- **المجموعة الأولى** : تضم ١٠ مرضى بالتليف الكبدي و الاستسقاء و يعانون من الالتهاب البريتوني البكتيري التلقائي و الفشل الكبدي الكلوي.
- **المجموعة الثانية** : تضم ١٠ مرضى بالتليف الكبدي و الاستسقاء و يعانون الالتهاب البريتوني البكتيري التلقائي مع وظائف كلى طبيعية.

# دور أول أكسيد النيتريك في اضطراب وظائف الكلى في مرضى الالتهاب البريتوني البكتيري التلقائي

رسالة مقدمة
توطئة للحصول على درجة الماجستير في
الباطنة العامة


مقدمة من
الطبيبة / وسام أحمد إبراهيم
بكالوريوس الطب و الجراحة


تحت إشراف


**أ.د/ محمد علي مرعي مخلوف**

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أستاذ مساعد الباطنة العامة

كلية الطب – جامعة عين شمس

**د/ إيهاب حسن نشأت**

مدرس الباطنة العامة

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